ULTRASOUND MEASUREMENT OF OVARIAN VOLUME AND ANTRAL FOLLICULAR COUNT IN NORMAL (FERTILITY –PROVEN) AND INFERTILE SOUTH INDIAN WOMEN (CHENNAI)

A CASE CONTROL STUDY

Dissertation submitted to

THE TAMILNADU
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In partial fulfillment of the requirement
for the award of

M.S.DEGREE – BRANCH - II
OBSTETRICS & GYNECOLOGY

GOVT. KILPAUK MEDICAL COLLEGE
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BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"ULTRASOUND MEASUREMENT OF OVARIAN VOLUME AND ANTRAL FOLLICULAR COUNT IN NORMAL (FERTILITY PROVEN) AND INFERTILE SOUTH INDIAN WOMEN (CHENNAI)"** is the bonafide originalwork of **DR.OORVASI.S** under the guidance of**PROF DR.MALARVIZHI MD., DGO.,** Department of Obstetrics and Gynaecology, KMCH, Chennai in partial fulfilment of the requirements for MS Obstetrics and Gynaecology branch II examination of the TamilnaduDr.MGR Medical university to be held in April 2016 .The period of Postgraduate study and training from June 2013 to April 2016.

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DECLARATION

I solemnly declare that this **dissertation "ULTRASOUND MEASUREMENT OF OVARIAN VOLUME AND ANTRAL FOLLICULAR COUNT IN NORMAL (FERTILITY PROVEN) AND INFERTILE SOUTH INDIAN WOMEN (CHENNAI)**wasprepared by me at Government Kilpauk Medical College and Hospital,Chennai, under the guidance and supervision of **Dr.MALARVIZHI MD., DGO.** Professor, Dept of Obstetrics and Gynaecology,Chennai. This dissertation is submitted to **The Tamil nadu Dr. M.G.R.Medical University, Chennai** in partial fulfillment of the University regulations for the award of the degree of **M.S. (Obstetrics and Gynaecology).**

Place: Chennai
Date: **(Dr.S.OORVASI)**

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I start this thesis in the name of Almighty God, the most beneficent and forgiving. I thank God for giving me the privilege to learn from the able teachers in my department.

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INSTITUTIONAL ETHICAL COMMITTEE
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Protocol ID. No.2/05/2015 Meeting held on 07/05/2015
CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "Ultrasound measurement of ovarian volume and antral follicle count in normal (fertility-proven) and infertile women in south Indian population (Chennai) – For Dissertation Purpose" submitted by Dr.S.Oorvasi, Post Graduate in MS (O&G), Govt. Kilpauk Medical College, Kilpauk, Chennai-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

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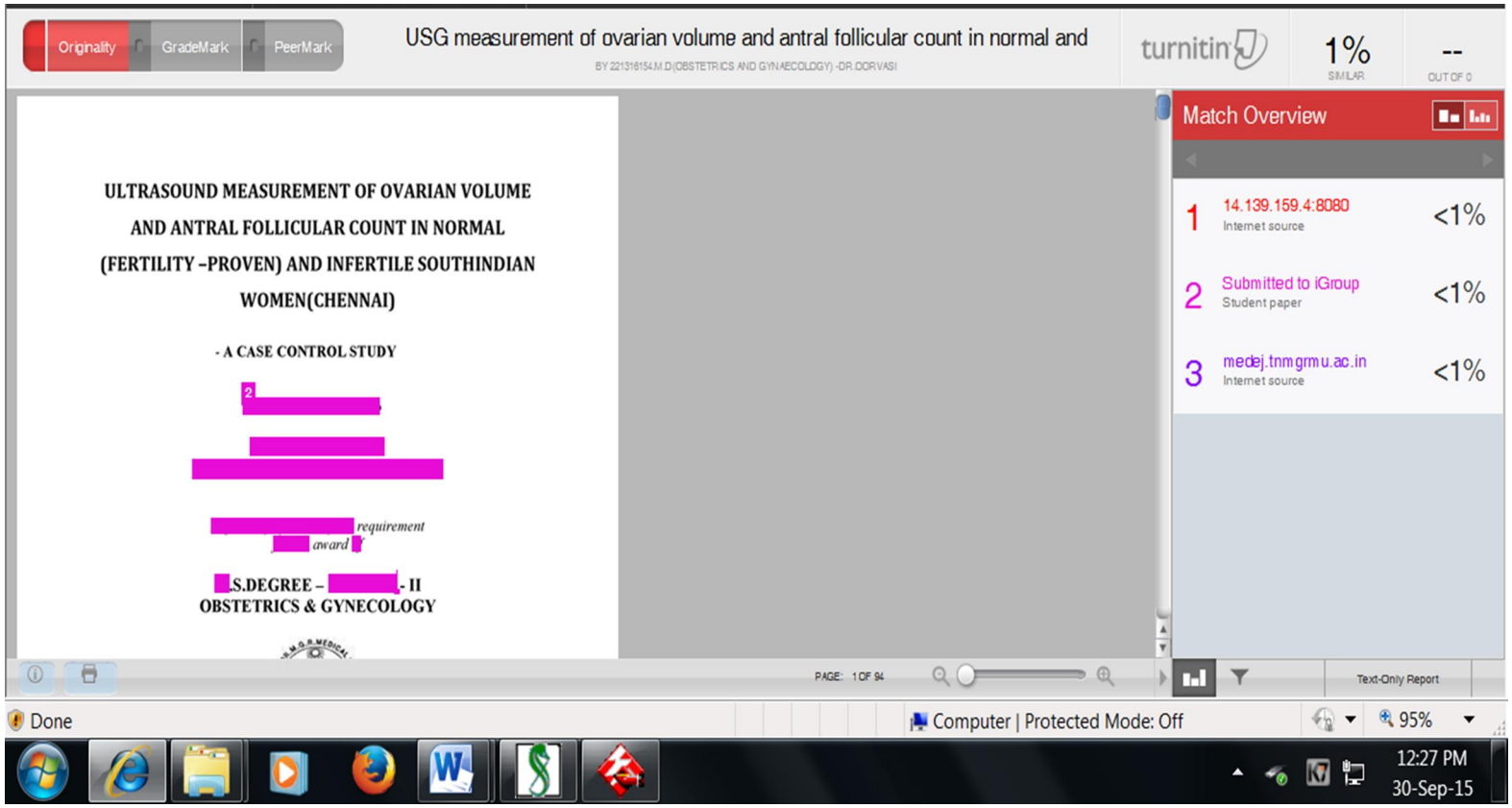
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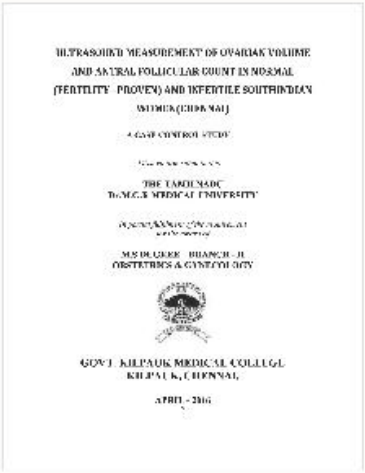

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INTRODUCTION

INTRODUCTION

INFERTILITY

Infertility is the failure of a couple to conceive after 1 yearof regular, unprotected intercourse. Ovulatory disorder isone of the most common reasons of female factor infertility30% of all cases).[1]

OVARIAN RESERVE

The term denotes the capacity of the ovary to provide egg cells which is capable for fertilization results in a good outcome which in turn means a successful pregnancy.With advanced maternal age the capability of the ovary to produce egg cells will decline, constituting a major factor in the inverse correlation between age and female fertility.However, between women of the samechronological age, the quantitative ovarian reserve mayvary substantially. To assess the individual quantitativeovarian reserve[90], various ovarian reserve tests (ORTs)have been developed, viz. (1) day‐3 follicle stimulating hormone (FSH), (2) anti‐Mullerian hormone (AMH)and (3) antral follicle count (AFC).

ANTRAL FOLLICLE COUNT

Antral follicular count is referred as a number of oocytes and follicles in ovaries which is morphologically healthy and associated with serum concentrations of anti mullerian hormone. Anti mullerian hormone is a marker of quantity of healthy follicles and oocytes in ovaries. Antral follicular count measured by serial transvaginal ultrasonography during follicular phase is reproducible within an individual.

OVARIAN VOLUME

Ovarian volume is an important tool in the screening, diagnosis and monitoring the treatment of conditions such as polycystic ovarian syndrome, ovarian cancer and adolescent abnormalities in reproductive medicine. Recent advances in technology, including the transvaginal scan have made possible the measurement of ovarian volume both easy and cost effective .Measurement of ovarian volume has a role in the assessment of ovarian reserve and prediction of response to superovulation.

Reproductive aging is considered to bethe consequence of a decrease in the quantity and qualityof the ovarian follicle pool.[1‑3] Autopsy studies of humanovaries show that the number of follicles decreases rapidlywith female age, starting in fetal life and continuing untilafter menopause.The number of antralfollicles and the total ovarian volume as measured bytransvaginal USG have been mentioned in the literature topredict declining fertility related to

reproductive aging.[4‑7]Studies concerning physiological ovarian aging in womenwith and without fertility problems are very limited and mostof them are done in Western countries. It, therefore, seemswarranted to evaluate the aforementioned sonographictest parameters in women of different ages in India.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

INFERTILITY

Infertility is a major distress to many couples in the world,causing increased members of them to approach medical care. Most people have decreased fertility rate , than total sterility ,these people are likely to conceive spontaneously with minimal efforts . Development in assisted reproductive technologyhas encouraged the use of newer techniques into routine practice reducing many investigatory procedures and the time delay . The desire for children is usually stronger in women than men and urge to conceive immediately after marriage by their family adds up the stress factor .Hence childbearing is more important to women than the claims of their career .Infertility is a tragedy to the married woman and can be lead to marital upset , personal disturbances and poor health. Childlessness may result from recurrent abortion and stillbirth but the commonest cause is a failure to conceive.

DEFINITION

Infertility[1] is by definition , the failure of the couple to be able to conceive spontaneously after 1 year of unprotected natural intercourse.

- ❖ It is broadly classified as Primary infertility and Secondary infertility.
- ✓ Primary infertility- in which the couple have never conceived

- ✓ Secondary infertility or sterility- the state of infertility developing after previous pregnancies .

- ❖ ***Subfertility*** - It refers to the couples who conceives after 12 months of attempted impregnation methods.
- ❖ ***Fecundability*** – is the probability of getting pregnant per menstrual cycle .
- ❖ ***Fecundity***- the probability of a couple to achieve a live birth per cycle .

All these conditions have equal chances to affect either the male or the female partner of a marriage. The normal couple has the fecundability estimated to be about 20 to 25 per cent . Based on this estimate , 90 per cent of couple will conceive spontaneously after twelve months of unprotected sexual intercourse.

Epidemiology

In the general population , the conception rate of couples is expected to be 84% within 12 months and to be 92% within 24 months of unprotected intercourse[8].

Factors essential for conception

- Healthy and motile sperms should be deposited near the cervix or high in the vagina(male factor) .

- The spermatozoa must acquire changes like capacitation , acrosomal reaction and motility in the female reproductive tract(cervical factor).
- The motile sperms have to ascend through the cervix and the uterine cavity to reach the fallopian tubes , the site of fertilisation.
- The fallopian tubes should be patent without any adhesions and the released ovum has to be picked up by the tube at the fimbrial end (uterine and tubal factors).
- Ovulation must have occurred(ovarian factor).
- The ovum should be fertilized by the sperm at the ampulla
- After fertilization, the embryo has to reach the implantation site (uterine cavity) within 3-4 days period .
- The endometrium of the uterine cavity should be made receptive by the hormones of reproduction , estrogen and progesterone and mediators like IGF-1 , cytokines and integrins , for implantation
- The corpus luteum should be able to function adequately till the placenta takes over its function .

ETIOPATHOGENESIS

Based on the etiopathogenesisand the prognostic factor ,Infertility is divided into five major categories .

Categories	Prevalence
Ovulatory factors	20 – 40%
Male factors	20 – 30%
Tubal factors	20 – 40%
Endometriosis	4 – 6%
Both male and female factor	10 – 40%
Unexplained	10 – 20%

With the differing environmental pattern and referral pattern among different population , the proportion of couples in each category differs . In general , the major determinants to have a spontaneous live birth in the infertile couples are maternal age , duration of infertility ,the number of pregnancies in the past and the cause of infertility . Interestingly, unexplained infertility got a better prognosis among these categories. Couple suffering from primary infertility of unexplained category of 2 years duration where the age of the female partner is twenty eight years, thecumulative live-birth rate in the next twelve months is 36%. Previous pregnancy in a infertile couple or a secondary infertility, shorter infertility durationand the female partner age less than 30 years , overall increase a women the chances oflive birth but the male side problems ,

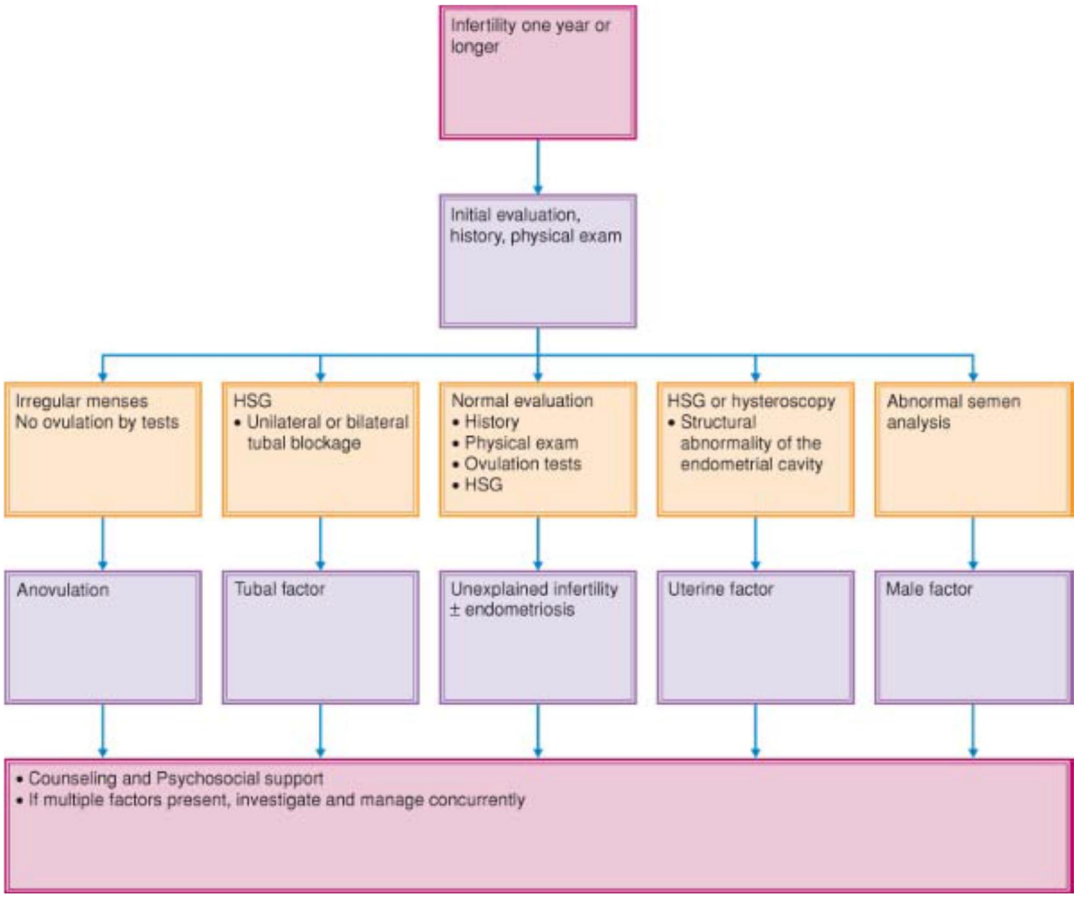
fallopian tube diseases andendometriosis considerably decrease it .Fertilityratealso varies in the sameindividual from time to time. These time factors arenot soobvious in the male exceptduring childhood and less absolutely in old age. But inthe female, time factor has a major role.

Physiological infertility in women is seen in the following periods

- Before puberty
- The period after puberty and before maturation fertility; that is upto 16—17 years of age, having a low fertility rate despite of regular menstrual cycle, the exact reason is not known and it is correlated to be due to anovulatory menstrual cycle in the initial few menstrual cycles
- Duringpregnancyperiod, when the ovulation is suppressed
- During lactation due to lactational amenorrhoea
- Before the menopause - gradual decline in the fertility rates with increasing age .
- After the menopause

INITIAL ASSESSMENT

(Reference - BEREK'S AND NOVAK'S textbook for GYNAECOLOGY: 15th edition)



CAUSES OF INFERTILITY

- **Male factor infertility**

Male infertility[9] indicates the absence of sufficient number of competent sperms, thereby causing failure of the sperms to fertilize the ovum. The WHO has proposed a criteria for various parameters of normal semen. It is a useful reference point for interpreting the results from different laboratories.

The male partner is responsiblein a direct way for 20%of cases of infertility and plays a contributory role with their female partner in another 50% cases of infertility. In the United States[2], Europe and Australia decreased sperm density has been commonly observed as a major cause, whereas decreased motility and semen volume are commoner inIndia.

The WHO compiled the following factors responsible for infertility in males[54]. The classification has to be updated with the recent advances,especially the factors responsible for defective spermatogenesis.

PRE-TESTICULAR	TESTICULAR	POST-TESTICULAR
ENDOCRINE : • Gonadotropin deficiency • Thyroid dysfunction • Hyperprolactinaemia • Obesity PSYCHOLOGICAL: • Erectile dysfunction • Impotence DRUGS : • Antihypertensives • Antipsychotics GENETIC : • 47XXY • Y chromosome deletions • Single gene mutations	• Immotile cilia syndrome • Cryptorchidism • Infections (mumps orchitis) • Toxins: drugs , smoking , radiation • Varicocele • Immunologic • Sertoli cell only syndrome • Primary testicular failure • oligoassthenoteratozoospermia	obstruction of efferent duct

SEMEN ANALYSIS

- ***Terminologies :***

- **Normo-zoospermia** - all parameters are normal

- **Oligo-zoospermia**[11] - decreased number of sperms

  Mild to moderate oligozoospermia : 5–20 million sperms per ml of semen

  Severe oligozoospermia : less than 5 million sperms per mL of semen

- **Astheno-zoospermia**[12]- decrease in the motility of sperms.
- **Terato-zoospermia** - increased number of abnormal forms of sperm
- **Oligoasthenoteratozoospermia** - all sperm parameters are abnormal
- **Azoospermia** - absence of sperm in semen
- **Aspermia (anejaculation)** – absence of ejaculation (ejaculation failure)
- **Leucocytospermia**- increased number of WBC's in semen
- **Necrozoospermia** - all sperms are either non-motile or non-viable .

Normal Seminal Fluid Analysis(WHO2010 guidelines):

- volume more than 1.5 mL[13]
- sperm concentration more than 15 million/mL
- sperm motility more than 32% progressive
- morphology[27] more than 4% normal forms (strict criteria)
- white blood cells count less than 1 million/mL

Immunobead or mixed antiglobulin reaction testa <10% coated

aTests for the presence of antibodies coating the spermwith permission.

Frequency of Some Etiologies in Male Factor Infertility

Cause	*Percentage*	*Cause*	*Percentage*
No identifiable cause	48.5	Varicocele	37.4
abnormal semen of unknown cause	26.4	Idiopathic	25.4
Varicocele	12.3	Testicular failure	9.4
Infectious causes	6.6	Obstruction	6.1
Immunologic causes	3.1	Cryptorchidism	6.1
Other acquired causes	2.6	Low semen volume	4.7
Congenital causes	2.1	Semen agglutination	3.1
Sexual factors	1.7	Viscosity of semen	1.9
Endocrine abnormalities	0.6	Others	5.9

Anti -sperm antibodies

The anti-sperm antibodies[32]particularly that are found on the surface of the sperm are associated with decreased pregnancy rates. Hence, testing for these antibodies is indicated in a person with a history of distal duct obstruction, previous genitalinfection, trauma to testis and with history of vasectomy reversal surgery.

Therapeutic drugs interfering with male infertility

- **Drugs causing defectivespermatogenesis** - methotrexate , sulfasalazine , nitrofurantoin , colchicine , chemotherapeutic drugs.
- **Pituatory suppressors –**GnRH analogues and testosterone injections.
- **Anti-androgenic drugs** – cimetidine , spironolactone .
- **Drugs causaing failureof Ejaculation**– α-blocking agents, anti-depressants, phenothiazines.
- **Drugs causing erectile dysfunction** – β-blocking agents , thiazide group of diuretics and metoclopramide.
- **Drug of abuse**–cocaine[20],heroin,cannabis and anabolic steroids.

Paternal age

Fertility rates are decreased withincreased paternal age older than 40-45 years and specifically over 50years of age[13]. The reason for this association is increased paternal age causes increasednumber of chromosomal abnormalities like trisomy 21and various autosomal dominant diseases like achondroplasia , craniosynostotic conditions and therfore associated with recurrent pregnancy loss leading to decreased fertility rates .

Management

Management options include

- Medical management[44] of hormonal abnormalities (exogenous FSH and clomiphene citrate)
- Treatment of sexually transmitted diseases.
- Varicocele repair
- Artificial insemination (with patient's own sperm in oligozoospermia and in cases of azoospermia seen in cystic fibrosis and some genetic defects ,the sperm for insemination is obtained from donor) .

OVARIAN CAUSES

FEMALE AGE AND DIMINISHED OVARIAN RESERVE

A strong association between increasing age of the infertile women and decreasing fertility rate has been documented well. The probability to become pregnant begins to declinein the early thirties and increases during the late thirties and early forties. In both spontaneous and ART cycles,Chronologic age of the mother is thestrongest predictor of ovarian reserve and also the major determinant of reproductive success. However, increased maternal age per sehas not traditionally been considered as a reason for infertility because it implies a physiologic condition than a pathologic condition. A study conducted to assess the fecundability of a woman who underwent artificial insemination with donor sperm dueto azoospermia in their spouse provided the majorinsight

into the effects of maternal age on their fertility rate. It has been found that fertility rates of women began to drop after the age of 30.After 1 year of inseminationsprocedure, the pregnancy rate in women aged 30 years and younger was 74% and decreased to 62% in women aged between 30 to 35 years, and considerably dropped to 54% in women more than 35 years of age.

Another insight into this decreasing fertility in aging women has been provided by the oocyte donation programs. Here they retrieved the embryos from a young women and transferredthem into an older women and observed that the pregnancy rate in the older women were equal to those of that the young women. The variation in pregnancy rate was directly related to donor's age rather than recipient'sage.

Among 260 egg donors with average age of over 30 yearswho had undergone COH with exogenous gonadotropins,the oocyte retrieval percycle declined steadily and the rate of decrease is 0.24 oocyte/year of increasing maternal age . These data strongly support that the age of the oocyte accounts for the major age–related decrease in female fertility rate rather than the age of the endometrium. And so, thedecreased ovarian reserve is the oocyte related decrease in fertility.

OVARIAN RESERVE

Ovarian reserve is the size and number of resting or non –growing primordial follicle population that presumably determines growing follicles numbers and the reproductive potential of the oocytes.So Ovarian reserve plays a major role in the ovaries responding to the exogenous gonadotropins administration in termsof the number of oocytes produced , follicle count , serum estradiol level and the quantity and duration of exogenous gonadotropins which is required for stimulation.

The screening tests which are used in the estimation of ovarian reserve include estimation of serum FSH (follicle stimulating hormone) level on day 3, serum inhibin B level[94] , serum MIS level (mullerian– inhibiting substance[63]), CCCT (*clomiphene citrate* challenge test) and ultrasound parameters including ovarian antral follicle count and the mean ovarian volume measurement done transvaginally.

Measurement of day 3 FSH

This test is based on the fact thatsmall increase in serum basal FSH levels correlates with the decreased fecundability seen in women in their late 30s. Following pituitary desensitization in women undergoing IVF treatment,assessment of basal FSH level is a better predictor of ovarian responsethantheir age.

Basal estradiol level

The estimation of estradiol level in day 3 of cycle correlates more with the follicular growth rather than the number of antral follicles. Early follicular estradiol levels are specifically high in older women and also in women with advanced reproductive age .

Clomiphene citrate challenge test

Clomiphene citrate has antiestrogenic effects on the hypothalamo - pituitary axis. It causes decrease in the suppression of FSH production by the pituitary. This test involves the measurement of both serum FSH and estradiol on day 3 and on day 10 afteradministring 100 mg of clomiphene citrate orally on each day from days 5 to 9. Depending on the assay used and the population screened,FSH levels vary so itis advised that each ART center have its own reference range for estimating theFSH levels.In a general infertility women population, the incidence of an abnormal CCCT is less than 10% in patients of 35 years of age or younger thatn that and the incidence raises to 26% in patients more than 40 years of age . The sensitivity of Basal day 3 FSH testing in identifying women who will not conceive with subsequent IVF treatment is only 8%and by the addition of the CCCT to this day 3 FSH testing increases the sensitivity of this prediction toonly 26%. However boththese tests, day 3 FSH and CCCT results combinedly give a high specificity of 96% in predictingthe IVF outcome. Hence in women with advanced age more than 40

years and with abnormal basal day 3 FSH or CCCT resultscan be advised to limit the number of IVF cycle attempts because of their overall poor prognosis. Howeverin youngerwomen less than 40 years of age and with regular menstrual cycles with abnormal day 3 FSH and CCCT tests, it is more difficult to interpret the prognosis . A retrospectivestudy has demonstrated that the ongoing pregnancy rate is 47% in women with regular cycles with their FSH levels ranging between 10 to 15 IU/L and in thosewomen, with FSH levels greater than 15 IU/l ,the pregnancy rate is only 28%. Therefore high basal FSH values cannot be used as the only basis for excluding women from the consideration for ART. Due to this variable nature of FSH while using as a screening test before COH, the need to search for other assays has been intensified.

Serum inhibin B

Inhibin B is secreted by ovarian granulosa cells from the preantral follicle stage. This secretion increases during the transition between the luteal and the follicular phasesof menstrualcycles,and hence it reflects the overall granulosacell function of the group of follicles that are recruited to undergo gonadotropin–dependent growth . This finding provided the flatform to investigate the potential roleof inhibin B as a prognostic marker in estimating ovarian response in ART cycles. It suppresses FSH production by the pituitary gland. In the CCCT, the suppression of FSH is done through inhibin B production by the granulosa cells. But still, the basal inhibin B levels are under

debate for use as a predictor of pregnancy outcomes. However many studies have shown that thestimulated inhibin B levels has a value in the management of COH cycles. The largest among these studies done in54 patients undergoing IVF , evaluated the levels of inhibin B after 4 days of gonadotropin stimulation and found that the Patients with inhibin B levels of less than 400 pg/mL, they had a significantly less number of follicles and oocytes. This thresholdvalue indicates that this stimulated inhibin B yielded a positive predictive value (PPV) of 86.7% in estimating ovarian response to exogenous gonadotropins.

Serum Antimullerian hormone (AMH)

AMH[94] has also been investigated as a marker for testing ovarian reserve and for estimating the ovarian responsiveness to stimulation. The granulosa cells of both preantral and small antral follicles produce this AMH. Its function is to inhibit the initiation of growth of the primordial follicle. In women with regular cycle, the serum level of AMH declines with age and it becomes undetectable by menopause. Also as the primordial follicle count decreases, the serum AMH concentration also decreases and hence making this hormone an ideal parameter for the early diagnosis of ovarian reserve depletion. Decreased levels of AMH in the early follicular phase correspond to poor ovarian reserve in ART cycles. A retrospective study conducted between normalandpoor responders with gonadotropin stimulationhave established a threshold value of 8.1 pmol/L . It predicted poor ovarian response with a

sensitivity of about80% and a specificity of about85%during a subsequent IVF cycle.

Antral follicular count

Antral follicular count[94] is measured byusing transvaginal ultrasound in the early follicular phase. All ovarian follicles measuring between 2 -10 mmin both ovaries are counted and the total value obtained is called basal antral follicle count(AFC). The AFC correlates with chronological age in normal women.It reflects the remains of the primordial follicular pool at that age.Decrease in AFC with increasing age ismore gradual rather than sudden. A low AFC is a major factor in establishing poor ovarian reserve and is usually accompanied by high levels of follicular stimulating hormone (FSH). Many studies have shown that AFC testing is far more accurate than that of basal FSH testing in older women while predicting IVF outcome[61].

The major determinant for the success of ovarian hyperstimulation is the estimation of AFC. Some suggest that the antral follicles measuring 2-5 or 4-6 mm in diameter is preferable. But, the no of smaller antral follicles of size 2-5mm highly correlates with the total no of antral follicles of size 2-10mm, and therefore it is suggested that counting all antral follicles of size 2-10mm indiameter is the most practical method for assessment of AFC in clinical settings. The intra and inter observer variability that occur while estimating the

AFC can be largely reduced by a newer technique called three dimentional automated follicular tracking.

Treatment of Diminished Ovarian Reserve

The ideal diagnostic marker for ovarian reserve is one which can be performed in women in basal state. It should have high sensitivity and specificity in identifying patients who will have live pregnancy outcomes. Efforts have been going on to identify such a prognostic test so that the patients can be counseled properly regarding the various treatment options.

Treatment for patients with diminished ovarian reserve is mainly IVFdone using donor oocytes or embryos andadoption. Patients undergoing IVF can be pretreated with dehydroepiandrosterone (DHEA) of about 25 mg thrice dailyfor 4 to 5 months to improve the oocyte yield and pregnancy rates.

IMPORTANCE OF OVARIAN VOLUME

The human ovary is the organ responsible for most of the changes, structural as well as behavioral, in a female starting from puberty through her reproductive age till menopause. Ovarian volume is an important tool in the screening, diagnosis and monitoring the treatment of conditions such as polycystic ovarian syndrome, ovarian cancer and adolescent abnormalities in reproductive medicine. Recent advances in technology, including the transvaginal scan have made possible the measurement of ovarian volume both

easy and cost effective .Measurement of ovarian volume has a role in the assessment of ovarian reserve and prediction of response to superovulation.

Technological improvements in ultrasound machines and the use of high frequency vaginal probes allow the investigators much closer access to ovaries. Thus we can get high quality images with good resolution. Scanning of the ovaries is now a routine tool of every infertility clinic worldwide to such an extent that operating in this field without ultrasound scanning is unthinkable. It is crucial in assessing the number and size of developing follicles in natural and stimulation cycles; the most important decisions when monitoring the cycle, such as adjusting the stimulation dose, timing the human chorionic gonadotropin(HCG) injection and oocyte recovery, are according to scan results. However, measuring the ovarian volume and estimating its size are not common practice, nor is the relevance of ovarian size and its clinical implications in normal and pathological conditions clear.

Ovarian volume throughout life

Childhood[69]

The human ovary is an organ which changes in size and activity throughout life. At birth, the ovary is ~1cm in length and weighs <0.3g. It has an elongated flattened shape that lies above true pelvis (Clement 1991). The ovary is a composite of four embryological determinants: (i) germ cells, (ii) granulosa cells (iii) germinal epithelium and (iv) mesenchymal stroma. The ovary decreases slightly in volume at 1 month of age, probably due to the

clearance of maternal oestrogen from the female neonate (Haber and Mayer 1994). Ovaries show a slow growth during the period of childhood. An increase in weight by 30-40 folds is noticed. They reach the size, shape and weight of the adult ovary, by the time she reaches puberty and lie within the true pelvis. Ivarson *et al* in 1983 demonstrated that there was an increase in mean volume of ovary from $0.7cm^3$ to $5.8cm^3$ through 10 years to 17 years of age.

Griffin *et al* (1995a) carried out ultrasound scans on 153 normal girls aged between 3 days and 14.9 years and showed an exponential increase in ovarian volume with age. Significantly in this study, no relationship with pubertal stage could be demonstrated. Orbak *et al (*1998) performed pelvic ultrasound in 75 girls in their puberty and showed a positive correlation between uterine length, fundal/cervical ratio,right ovarian volume and follicle stimulating hormone (FSH), luteinizing hormone (LH) and oestradiol concentrations to Tanner score. The best correlation was between pubertal stage and oestradiol concentrations.

Reproductive age

Adult ovaries are ovoid, measure approximately 3-5cm by 1.5-3cm by 0.6-1.5cm and weigh 5-8g. In early reproductive life they have a smooth white-pinkish exterior which later in life exhibits increasing numbers of retracted scars and convolutions[69]. There are by now three ill-defined zones in the ovary;

an outer cortex, an inner medulla, and the hilus. Follicular structures (corpora lutea, corpora albicantia, and cystic follicles) are visible in the cortex and medulla. There are considerable variations in size and weight of the ovaries in different women, depending mainly on the follicular content, but it has been suggested that there are no major changes in ovarian volume during reproductive years in individual women until the premenopausal period (Christensen *et al*, 1997). Currently there are few publications on ovarian volume in normal healthy fertile women in their reproductive life (Andolf *et al* 1987; Granberg and Wikland, 1987; Pache *et al* 1992). Christensen et al measured the ovarian volume of 428 healthy women aged 14-45 who attended a family planning clinic. They found that the ovarian volume was not correlated to age, height, weight and parity. While the smaller ovary remained the same volume throughout the cycle, the larger ovary increased in size from the beginning of the cycle to day 19 and decreased thereafter, due to the development of the preovulatory follicle in that ovary. The ovarian volumes in women with intra-uterine devices were shown to be larger than in women on the contraceptive pills; moreover cycle variations in volume were not observed in the latter. Unlike Griffin *et al* who found that the right ovary was larger than the left one in childhood, they and others showed that both ovaries were similar in size (Andolf *et al* 1987 Granberg and Wikland, 1987; Cohen *et al* 1990; Pache *et al* 1992).

Menopause

Following menopause, the ovaries will shrink to about one-half of their size as seen in the reproductive period. They weigh 3-4g (Thatcher and Naftolin,1991). Most postmenopausal ovaries have a shrunken pyriform external appearance. They are firm and have a predominantly solid, pale cut surface, although small inclusion cysts may be discernible within the cortex. Small white scars (corpora albicantia) and thick walled blood vessels are typically present within the medulla (Clement 1991). Many luteinized and follicular cysts can be found in the perimenopausal ovary and they may be present for up to 10 years after the menopause (Bigelow 1958).

Andolf *et al* showed that the size of ovaries decreases in menstruating women over 40 years of age and that parity has no influence over this (Andolf *et al* 1987). Merz *et al* investigated 155 premenopausal women and did not find any parity related changes in the ovarian volume. However postmenopausal women had significantly smaller ovaries and women who were >5 years into their menopause had smaller ovaries than women <5 years from the menopause. Higgins *et al* also found a dramatic drop in ovarian volume at the menopause, with the average upper limit of normal falling from 18cm^3 in premenopausal women to 8cm^3 in postmenopausal women (Higgins *et al* 1989). Tepper *et al* suggested an ovarian size nomogram for postmenopausal women based on transvaginal examinations in 311 healthy women. They found a linear relationship between menopause age and ovarian volume. The mean ovarian volume dropped from 8.6cm^3 a year after the menopause to 2.2cm^3 15

years into menopause. Webba *et al* compared 98 postmenopausal women to 40 women with regular periods and showed a decrease in ovarian volume after the first year of menopause followed by slow and gradual shrinkage thereafter, and more significantly after 4 years into the menopause. Botsis *et al* demonstrated that the reduction in ovarian volume isprevented, at least temporarily, in women treated by hormonal replacement therapy.After 6 months of transvaginal treatment with low dose estrogen, there was no change in the ovarian size.

Measurement of ovarian volume by transvaginal ultrasound

It is well accepted that transvaginal sonography[73] is superior to abdominal scan in imaging the pelvis because of the close location of the vaginal probe to the ovaries and the higher frequencies in use. The results are improved resolution and better quality of images and the inadequacy due to overlying abdominal fat and the discomfort of full bladder are avoided. The procedure is safe and the examination time by experienced sonographers is relatively short: no more than 10 to 15 min.

Saxton *et al* demonstrated that ovarian size can be measured accurately. They performed vaginal sonography[71]in women immediately before oopherectomy and measured the size of the ovaries in the laboratory and found comparable results. Intra and inter observer variations are very small in sonographic measuring of the ovaries. In the majority of the studies the ovaries are measured in three planes and the ovarian volume was calculated using the prolate ellipsoid formula V=D1xD2xD3x0.523. D1, D2 ,D3 are the three

maximal longitudinal antero-posterior and transverse diameters respectively. Recently a few investigators have suggested using computerized three dimensional transvaginal ultrasound. They found a higher degree of reproducibility of ovarian volume measurements, in addition to the advantage of online storage facility of images, by using this method. This technique is superior to 2D scanning in evaluating follicular volume. However it is a relatively new technology and not yet in widespread use only measurements of ovaries not containing cysts or large follicles will achieve an accurate net ovarian volume. Therefore in most of these studies, only ovaries with follicles of greater than 10-15mm were included. However, maximum follicular size eligible for ovarian volume measurement without skewing the net results is not clear.

Ovarian volume in assisted conception

Ovarian volume as a predictor for response to superovulation

The ovarian ability to respond to exogenous gonadotropic stimulation and to develop follicles simultaneously is mandatory for the successful outcome of in vitro fertilization. Failure to respond is common, particularly in older women upto 40% of whom will have their cycles cancelled. It is important for patients and clinicians to be able to assess the adequate ovarian response beginning treatment.

The relationship between increased female age with diminished ovarian function and elevated basal FSH concentration with a decreased chance of success with IVF is well established. This diminished ovarian 'reserve' is due to reduced numbers of primordial follicles from >250000 at menarche to a very few at the end of reproductive life. This loss starts around the age of 37 years and the menopause proceeds by 10-12 years. But there is a variation in the rate and number of depletion of follicles.Menstrual regularities and age alone are unreliable predictors of ovarian reserve. Follicle stimulating hormone (FSH) concentrations in follicular phase are not accurate indicators of normal or impaired ovarian function.

Measurement of serum estrodiol along with FSH may improve the prediction of fertility compared with basal FSH and chronological age alone.

Another test for ovarian reserve is the early follicular phase serum inhibin-B . now a days some of the higher tests such as the clomiphene challenge test developed by Navot *et al* and gonadotrophin release hormone agonist test have been shown to be superior to basal FSH serum concentrations in predicting response to stimulation.

There is a strong correlation between the ovarian volume and the number of primordial follicles in the ovarian tissue of women>35 years of age

(Lass *et al* 1997b). but there is no difference between the ovarian volume of fertile and non fertile group.

Syrop *et al* 1995; Lass *et al* 1997a; Tomas *et al* 1997 have investigated the relationship between ovarian volume and response to superovulation in IVF treatment. In all the studies there is one formula called the prolate ellipsoid formula was used to calculate the volume of the ovary and the results given as the mean ovarian volume , total ovarian volume and smallest ovarian volume. The most common definition of small ovaries is less than the mean volume minus one standard deviation.

Syrop *et al* found similar higher cancellation rates and fewer oocytes from women when their smallest ovary was<3cm$^{3.}$ In a further extended study they concluded that age and smallest ovarian volume are significant separate predictors for recovery of fewer than 8 mature oocytes. These two factors together had 75% sensitivity and specificity in predicting low numbers of oocytes recovered. The investigation of 166 infertile women undergoing IVF was done by Tomas *et al.* They counted the number of small follicles 2-5mm and measured the ovarian volume before gonadotropin stimulation. Patients were divided into three groups; patients with inactive ovaries (having <5 follicles in both ovaries), with normal ovaries (having 5-15 follicles) and those with polycystic ovaries (having >15 ovaries).

It was concluded that ovarian volume was correlated with the number of small follicles but not with the number of oocytes retrieved. Significantly the number of small follicles before stimulation was a better predictor than ovarian volume or age alone. Women with inactive ovaries by vaginal scan will have a poor response to ovarian stimulation. Pellicer *et al* have studied 18 younger women; 10 were known to be poor responders and eight were controls with adequate responses in the past .They measured the ovarian volume by three dimensional vaginal scan , could not find differences in ovarian volume between the two groups but the number of small follicles were lower in the poor responders group.

The authors did not find differences in ovarian volume in this particular population. First, it was a simple sample; second, young low responders may have diminished ovarian reserve without evident change in ovarian volume. Ovarian size is not a predictor of clinical pregnancy rates despite reduced responses to superovulation in women with small ovaries. However, Syrop *et al* studied 261 patients and found a decreased pregnancy rate in women who had ovaries of $<3cm^3$. The conclusion of these studies is that ovarian agring is reflected by decreased ovarian volume and can be observed earlier than a rise in FSH concentrations.

Ovarian volume measurement is quick and cost effective.Transvaginal ultrasound is used to measure the ovarian volume in all patients before

ovulation induction regardless of age, and stimulation protocols. Women having a mean ovarian volume of <3cm^3 have a higher chance of follicular stimulation failure.

Ovarian volume and hyperstimulation syndrome

The size of ovaries plays an integral role in the diagnosis of OHSS and is useful for grading the severity of it. The first to show that the measurement of total ovarian volume before giving HCG in IVF cycles may help to predict the risk of developing moderate or severe OHSS was Oyesanya *et al* Utilization of ultrasonographic techniques to follow the developing follicles in fertile cycling women was done by Gore *et al*. They characterized individual follicles as dominant, subdominant ovulatory and atreic follicles by their size shape echogenicity and growth dynamics and demonstrated and association between cycle outcome dominant and subdominant follicles. Danninger *et al* took one step further and investigated the correlation between ovarian volumes measured by 3D vaginal scan on day 1 of stimulation to the development of moderate to severe OHSS in 101 women without polycystic ovaries. They found that the baseline ovarian volume was significantly greater in patients who later developed OHSS than in patients who did not (13.2 versus 8.9cm^3, respectively P=0.035).

These results indicate that ovarian volume is a useful tool for predicting both over and under-responsiveness to superovulation. Women with significantly small ovaries should be counseled about the risk of a suboptimal response to stimulation even if other screening tests such as base line FSH are normal. On the other hand, women with relatively large ovaries, without the typical polycystic appearance, should be warned that they may respond excessively. So far, there have been no published studies in which ovarian volume measurements were taken into account when deciding on the stimulation protocols and dose of gonadotrophin.

Ovarian volume and Doppler blood flow

Since the introduction of pulsed transvaginal colour Doppler[62], a number of researchers have investigated the blood flow in uterine artery and the implantation site. However, only very little information is available on the intraovarian or extraovarian blood circulation in the context of reproductive medicine. An increased blood flow within the leading follicle during the preovulatory phase in spontaneous cycles was observed by Campbell *et al*. Increased blood velocity during the day of ovulation, without differences between spontaneous and stimulated cycles was reported by Kupesic and Kurjak, even though it is difficult to detect minor changes in intraovarian blood circulation during the stimulated cycles(Tekay *et al* 1995).

Strigini *et al* showed that the intraovarian pulsatility index(PI) was significantly lower in FSH treated patients than in spontaneous cycles on the

day of peak oestradiol and concluded that the multiple follicular development is associated with a significant reduction in the impedance to perifollicular blood flow. Moohan *et al* on the same lines stressed that low PI (<0.75) and resistance index (RI, <0.48) are associated with severe OHSS. The measurement of intraovarian vascular resistance before transfer of embryo was recommended by them, especially for patients who are at risk of developing severe OHSS.

A few authors have studied the ability of intraovarian blood flow to predict IVF outcome (Tekay et *al* 1996). A negative correlation between the intraovarian PI and the number of follicles developed in IVF cycles was found byWeiner *et al* 1993. Tekay *et al* studied that the intraovarian PI of pregnant and non-pregnant patients undergoing IVF treatment was the same. 20 patients undergoing ovulation induction with clomiphene citrate and 11 patients having IVF were investigated by Lunenfeld *et al*. They measured blood flow at a few points throughout the treatment. Intraovarian flow was seen in 20% of women in the early follicular phase, in 56% during the periovulatory phase and upto 85% in the mid-luteal phase. There is a gradual decrease in the intraovarian PI from the early follicular phase to the periovulatory and mid-luteal phase. Balakier and Stronell measured the perifollicular peak velocity and /ri in 52 IVF cycles. A strong correlation between the ovarian follicle size and their peak velocity was found by them. High peak velocity was achieved after HCG injection and was related to patients' age but not to the maturity of the oocytes.

The increase in ovarian blood flow and the decrease in PI and RI during the stimulation phase and follicular growth are due to the developed perifollicular capillary network under the influence of FSH, oestradiol, progesterone or other angiogenic factors (Krannzfelder and Maurer-Shchultze, 1989; Lunenfeld *et al* 1996).Zaidi *et al* (1995) measured stromal peak systolic blood flow velocity on day 2-3 of cycles of PCOS patients and normal controls (Zaidi *et al* 1995). The clinical PCOS group (n=13) and PCO like by transvaginal scan (n=12) had a significantly higher Vmax than the control group (n=63), without any difference in the PI between the groups .This increase in stromal bloodflow velocity may explain the excessive response often seen during gonadotropin stimulation in patients with polycystic ovaries.

The changes in ovarian volume through life described above could be explained, atleast partially, as resulting from changes in bloodsupply to the ovary, but to the best of our knowledge there is no study that has investigated this hypothesis. We have shown recently (Lass *et al*., 1998b) that in 29 women who had unilateral salphingectomy before their IVF treatment, there were statiscally significant fewer follicles developed and consequently fewer oocytes were retrieved from the side of the operation in comparison with the side of the intact adnexa . However, ovarian volume was identical on both sides ($6.2cm^2$). The reduced no of follicles and oocytes might be explained by diminished bloodsupply to the ovary as a consequence of the surgery on the operated side,

but Doppler flow was not used in this study and it remains as speculation that requires further investigation.

OTHER CLINICAL IMPLICATIONS OF OVARIAN VOLUME MEASUREMENT

Ovarian volume as a marker for ovarian cancer

Pelvic examination, serum CA 125 and transvaginal sonography(TVS) are the most extensive methods for screening of ovarian cancer. Presently TVS screening is considered to be the most effective .Van Nagell *et al*, in his study performed transvaginal scan on 8500 asymptomatic women. If the volume of an ovary is >20cm^3 in premenopausal and >10 cm^3in postmenopausal women it was considered to be abnormal by them. In addition they looked for the presence of internal papillary projections. Of the 121 women with persistant abnormalities on TVS, eight had primary ovarian carcinoma that, except for one, could not be detected by physical examination and /or CA 125. Other have confirmed the benefits of TVS in screening for ovarian cancer and Zalel *et al* suggested that ovarian volume measurements should serve as the primary method of diagnosis of ovarian cancer.

ABNORMALITIES OF ADOLESCENCE

A number of studies measuring ovarian volume in adolescents with various disorders affecting reproductive function.

Precocious puberty and growth disorders

The measurement of volume of ovaries has been found to be useful in the diagnosis of precocious puberty; these girls had markedly increased ovarian volumes in comparison with a normal population (Bridges *et al*., 1995; Ciotti *et al*., 1995; Griffin *et al., 1995b; Haber et al*., 1995).This may also allow differentiation between true isosexual precocity when the enlargement of the ovaries is bilateral and pseudosexual precocity in which there is unilateral enlargement (king *et al., 1993).* Themeasurement of volume of ovaries is the most sensitive measure used in the interpretation of efficiency of GnRH analogue treatment of these cases.

Studies of girls with growth disorders by Bridges *et al* (1993): Tall stature, growth hormone (GH) insufficiencyand skeletal dysplasia showed that total ovarian volume of untreated GH insufficient girls is significantly less than either of the GH treated groups.

Comparison of ovarian volumes by Haber *et al (1995)* of 55 children aged 3 months to 7 years with premature thelarche to 101 age matched controls showed no significant differences between the two groups. This is in contrast to the studies by Bridges *et al. and* Griffin *et al* ., who demonstrated higher ovarian volume scores in girls suffering from this condition(Bridges *et al.,1995; and* Griffin *et al.,1995b).*

Menstrual disorders

The measurement of volume of ovaries is an accurate diagnostic tool for adolescent girls with irregular menses. In the majority of these girls, enlarged

ovaries are associated with PCOS (Herter *et al1996*). Girls with enlarged ovaries had the highest LH, testosterone and androstendione concentration. A substantial group of girls with irregular menses and initial normal ovarian volume will have enlarged ovaries in later scans; thus after the menarche, normal ovarian characteristics may suddenly change to a polycystic appearance and increase in volume (Venturoli *et al*., 1995).

Eating Disorders

Young anorexic girls have mean weights, weight/height ratios, ovarian and uterine volumes below normal (Lai *et al, 1994; Andolf et al, 1997;* Sobanski *et al, 1997*). After medical treatment, girls that resumed menstruation improved in all their parameters (Lai *et al*., 1994). Girls who gained weight had higher ovarian volumes. Young girls that achieved an increase in their ovarian volume did better in the long term than those who reached their desired weight without an increase in ovarian volume. Thus it is concluded that normalized ovaries indicated favorable physical recovery. Conventional target weight and weight/height ratio in anorexia nervosa may be too low to ensure ovarian and uterine maturity and that pelvic ultrasound is an useful addition to their management.

SUMMARY

In recent years, there has been a rapid increase in the use of trans-vaginal ultrasound in gynecology and reproductive medicine. Consequently, the measurement of volume of ovaries is emerging as a significant tool in the screening, diagnosis and supervising the treatment of conditions like PCOS, ovarian cancer etc. In Obstetrics it appears that volume of ovaries has a significant role in the assessment of ovarian reserve and predicting response to super-ovulation.

OVULATORY DISORDERS

Classification of disorders of ovulation(anovulation)

Group Site of lesionconcentration

Hypo-gonadotrophic Central low FSH

Hypo-oestrogenic low estrogen

Normo-prolactinaemic normal prolactin

WHO typeI

Normo-gonadotrophic hypothalamo pituatorynormal FSH

Normo-oestrogenic Ovarian axis normal estradiol

Normo-prolactinaemic normal prolactin

WHO typeII

HypergonadotrophicOvarian failure high FSH

Hypo-oestrogenic low estradiol

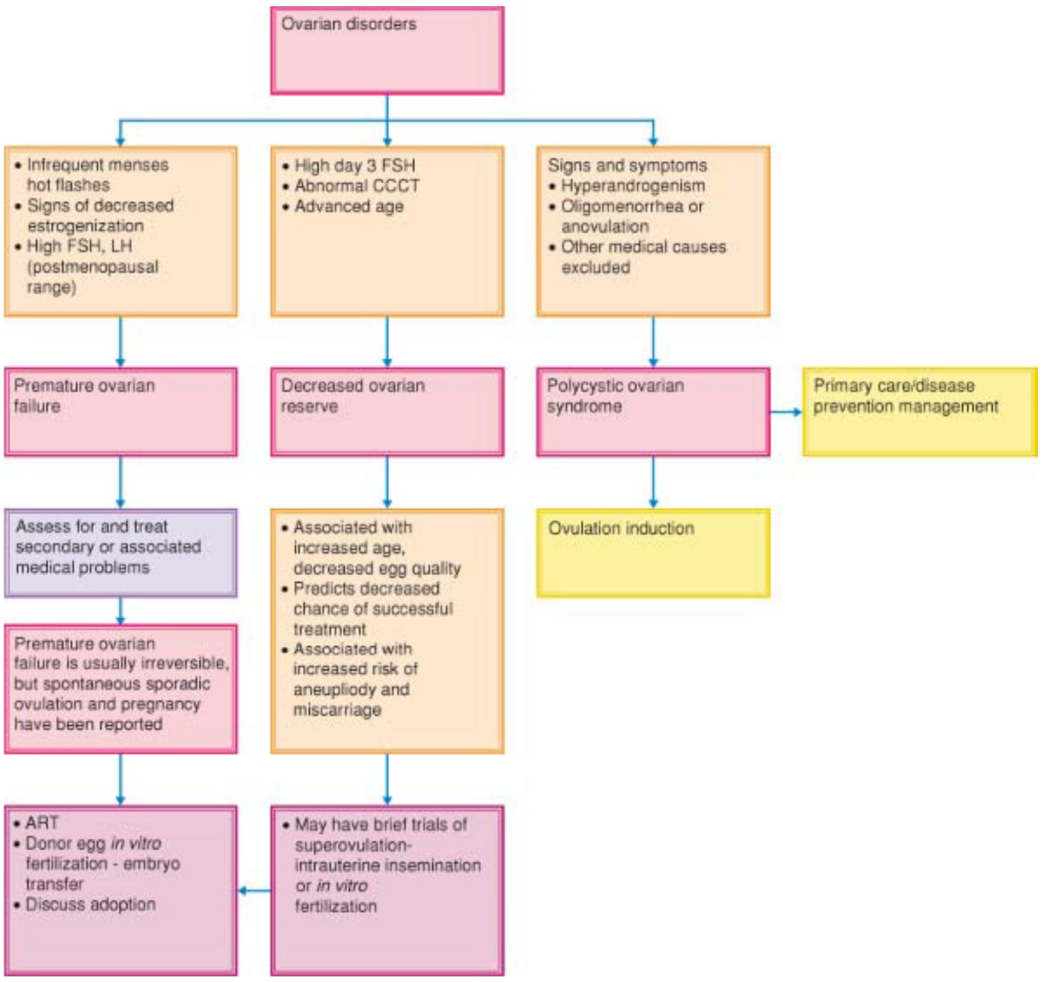
Normoprolactinaemic normal prolactin

WHO typeIII

Hyperprolactinaemic Central low FSH

low oestradiol

high prolactin



Anovulationor oligo-ovulation is seen 1/5 of women with infertility.Depending on the site, anovulatory infertilityfurther classified as follows :

HYPOTHALAMUS AND PITUITARY

(HYPOGONADOTROPHIC HYPOGONADISM)

(**WHO TYPE** I)

The abnormalities of Gonadotrophin releasing hormone

(GnRH) agonist secretion leads to low levels of estradiol, luteinizinghormone (LH) follicle stimulating hormone (FSH) [60].

- Kallman's Syndrome is one of the congenital cause of anovulation . It is manifested as anosmia with gonadotrophin deficiency. Acquired causes includes stress, excessive weight loss, heavy exercises,pituitary tumours, postpartum pituitary necrosis known as Sheehan's syndrome .

Clinical examination and imaging of the pituitary fossa is essential when a pituatory space occupying lesionis suspected.

NORMOGONADOTROPHIC HYPOGONADISM

Most common cause of normogonadotrophic anovulation is polycystic ovarian syndrome(PCOS).

Other conditionsincludeadrenaltumours ,congenital adrenal hyperplasia , and androgen producing ovarian tumours.

In the last 3 conditions, there will be a coexistent hirsutismand it requires more detailed investigations including 17-hydroxy progesterone, serumtestosteronelevels,dehydroepiandrostenedione sulphate(DHEAS) levels.

POLYCYSTIC OVARIAN SYNDROME(PCOS)

Polycystic ovary syndrome (PCOS) is the most common cause of oligo-ovulation and anovulation both in normal as well as infertile population. Clinicalfeatures are heterogeneous and it varies in the same individual over time. They may present with features like menstrual irregularities,anovulatory infertility,hirsutism and obesity.

The recently accepted criteria for the diagnosis ofPCOS are as follows:

The presence of any two of the following three features listed below is diasnotic of PCOS:

1. Oligo and/or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries

And there should be absence of other endocrine causes of infertility like

Congenital adrenal hyperplasia,Androgen secreting tumors,Cushings syndrome,

Hyperprolactinaemia andThyroid dysfunction.

The clinical indicators of hyperandrogenismincludesacne , hirsutism and androgenic alopecia . The increase in free testosterone or free androgen index (FAI) is the biochemical markers ofPCOS. Some womenwith PCOS may have only isolated elevations in dehydroepiandrosteronesulphate (DHEAS) level.

USG DIAGNOSIS OF PCOS

The definition of polycystic ovaries on ultrasound includes the presence of 12 or more follicles in each ovary measuringbetween2–9 mm in diameter with increased ovarian volume of more than 10 ml. The ovarian volume is usually calculated by using the formula 0.5 × length × width ×thickness.The distribution of folliclesin the ovary is not mentioned in the definition soonly one ovary showing the above described criteria is sufficient for thediagnosis.

Clinical Findings that Suggest Insulin Resistance and Hyperinsulinemia

The physical findings associated with insulin resistance,

- Body mass index >27 kg/m2
- Waist–to–hip ratio>0.85
- Waist>100 cm

- Acanthosis nigricans
- Numerous achrochordons or skin tags

HYPERGONADOTROPHIC HYPOGONADISM (WHO TYPE III)

Patients presenting with amenorrhoea with either a decreased or undetectable levels of oestrogen with increased levels of serum FSH indicates ovarian failure . The causes include gonadal dysgenesis , Turners Syndrome (XO), Turner mosaic(XO, XX,XX), autoimmune conditions,radiation and chemotherapy. In most of the cases, the cause remains unknown. Turner's syndrome is a choromosomal abnormality with 45 (XO) choromosome .The phenotypic features of turner's syndrome includesweb neck,short stature, shield shaped chest and cubitus valgus deformity. The gonads are 'streak' ovaries it means ovaries containing no functioning follicles when they attain the puberty age .Turner mosaics characterized by 45X or 46XX with or without normal ovulation and menstruation.

HYPERPROLACTINAEMIA

Elevated levels of serum prolactin interferes with the normal gonadrophin releasing hormonesecretion, causing anovulation and

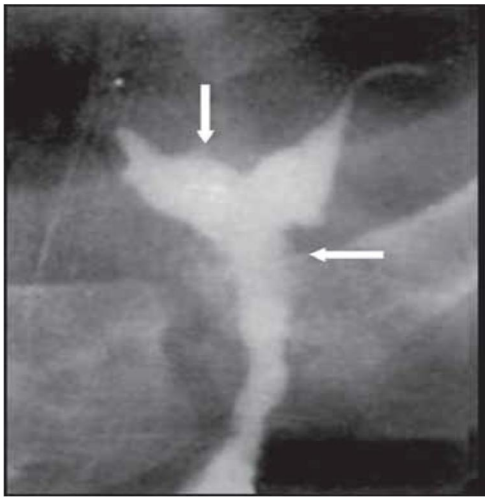
amenorrhoeaand galactorrhoea and are associated withlow levelsof serum oestradiol and FSH. Hyperprolactinaemia iscommonly seen in pituitary adenomas andother tumoursthat produce hormone prolactin so blocks the inhibitory action of the hypothalamus.

Other causesinclude primary hypothyroidism, chronic renal failure and drugs like combined oral contraceptivepill,dopamine depleting agents like methyldopa and reserpine , dopamine receptor antagonists like phenothiazines and metaclopramide.

TUBAL FACTORS

Both the peritoneal and tubal factors may contriute upto 35 % of total cases of infertility.Obstruction of the tubes of either completel or partial , occurs due to previous tubal infections or salphingitis following tubercular , gonococcal , chlamydial,puerperal and postabortal infections and non-infectious causes are endometriosis, tubal polyps , tubal spasm, salphingitis isthmica nodosa and intra tubal mucous debris. Tubal disease is the reason for 15–20 percent of cases of primaryInfertility and 40% cases of secondary infertility. It may be due to surgeries and pelvic infections that causes scarring , tissue damage and finally leads to formation of adhesion . This affects the tubal motility function resulting in eithertotalor tubal occlusion .The distal part of the tube is more commonly involved in obstruction, so fluid gets accumulated

within the tubes leads to hydrosalpinx. A fallopian tube depends only on the patency and the integrity of the mucosal lining for its normal function. So, damage tothe fallopian tubes are irreversible hence corrections can be verydifficult. Tubal diseases are best diagnosed by hysterosalphingography, laparoscopy, Chlamydia and serology.Treatment is depends upon which part of the tube gets affected. Proximal tubal catheterization or cannulation for proximal tubal occlusion, distal occlusion can be corrected by tubal microsurgery and fimbrioplasty.IVF is the treatment of choice for infertility patients with severe tubal damage.



PERITONEAL FACTORS

The pelvic adhesions preventthe tube from performing its normal function of picking up the released ovum during ovulation. It also creates a mechanical barrier between ovary and fimbriae . These adhesions may results from peritonitis following any cause most importantly they are associated with

appendicitisandfollowing puerperal and post abortal infections. Endometriosis is the cause for 15 % women with infertility.

ENDOMETRIOSIS

It is the presence of endometrial tissue outside the uterine cavity. The usual sites are the ovaries, pelvic peritoneum, and the rectovaginal septum. The prevalence rate of endometriosis with infertility in women is 21%. Women with endometriosis have a poor outcome after ART. A systematic review suggested that pregnancy rates have been halved in these patients while comparing them with those women with tubal causes of infertility. Also, data from previous studies also suggest poor oocyte and embryo quality, poor ovrian reserve and defective implantation in advanced endometriosis. Peritoneal fluid of patients with endometriosis contains increased levels of growth factors, cytokinesand activated macrophages. These are all toxic to the sperm function and theembryosurvival. Also, the theory of abnormal ectopic endometrial may cause implantation failure is also increasing now a days.

INFECTION

The principal reason behind tubal disease is pelvic inflammatory disease (PID) . It can occur spontaneously or as a complication following abortion, puerperium , intrauterine instrumentation and pelvic surgery. The incidence of

tubal infertility has been reported following one,two, three episodes of PID are 85, 19.5%, 40%. This risk is further aggravated by subsequent infections by organisms like *Chlamydia trachomatis* or *Neisseria gonorrhoea* . In Europe,Chlamydia is responsible for 50 percent cases of all PID and it is most common cause of sexually transmitted diseases. The factors that are associated with Chlamydia infection also increases the risk of tubal disease .These factors includefirst sexual intercourse at younger age , multiple sexual partners ,heavy alcohol and cigarette smokingand poor socio-economic status .

UTERINE FACTORS

- Complete absence of uterus and hypoplasia
- Submocous polyp
- Asherman's syndrome – intrauterine adhesions resulting from previous surgery in the uterus and curettage.
- Uterine fibroid
- Endometritis (tubercular)

CERVICAL FACTORS

- The thick cervical mucus may be due to the presence of local sperm antibodies or due to mid-cycle low pH of the mucus, so there is difficulty in ascending of sperm into the uterine cavity.
- Amputation of the cervix, cervical cone biopsies and excessive cervical diathermy leads to loss of cervical mucus.
- In retroverted uterus and in severe prolapsed, there is misdirection of cervical canal.
- Some of the women may have a tight internal os – cervical stenosis which needs to be dilated.

VAGINAL FACTORS

- Purulentvaginal discharge *:*clinical findings showed that many women presenting with chronic cervicitis and *Trichomonas* vaginitis are able to

conceive repeatedly without any difficulty ; some people contract gonorrhoea and pregnancy simultaneously!

- Vaginalseptum, tumours and vaginal membranes prevent the ascend of spermatozoa to reach the cervix.

COITAL DIFFICULTIES

1-2 per cent of those women with apareunia and dyspareunia seeking advice on account of infertilityare found to have not consummated on their marriage. Many of these women do not realize the fact nor do their husbands.

Frequency and Timing of Coitus

Coitus has to occur once in 48 hours during the fertile period for the optimum chance of conception. At the same time it won't be occur more frequently that too may account for infertility very rarely. Infrequent coitus during the period of ovulation alone is the more important cause for failure to conceive.

***Use of Lubricants*:**

Some patients may use lubricants in order to overcome the coital difficulties. They will use it to overcome the problems associated with dryvagina. These lubricants have a contraceptive action. Some of the jellies are acidic in nature, so they are spermicidal. The greases such as soft paraffin and lanolin causes spermatozoa to a standstillcondition.

SURGERY:

Mostlower abdominal and pelvic surgeries cause dense adhesions and hence it is a risk factor for infertility. Any surgery it may be gynecological or surgical like appendicectomy, bowel resection and urological operations , increases the risk of tubal disease that in turn leads to infertility.

OTHER CAUSES

Orgasm

It is not necessary for a woman to experience orgasm to conceive; so it may not be a serious issue.

Effluvium Seminis

Normally most of the semen ejaculated escapes from the vagina immediately after coitus. Patients might think this as the cause for being not able to conceive. *Effluvium seminis* is a normal phenomenon and doesn't cause infertility, since the amount of semen left behind is more than sufficient for fertilization. Only the sperm that enter the cervical mucus are able to fertilize the ovum and so the loss of the remaining semen is not significant. Moreover, spermatozoa accounts for about only 10 % of the total seminal fluid volume.

Anxiety and Apprehension

It is a common belief that extreme anxiety to conceive, lowers fertility and they are advised to adopt a baby in the belief that this will reduce anxiety and they will conceive spontaneously. But this fact has not been confirmed by any statistics.

Familial Disposition, Genetic and Constitutional Factors

It is observed that some families have a higher conception rate while some others have a lower rate and the various explanations offered is generally not clear. They say this infertility goes with obesity, heavy build andmasculine traits. But all these factors are merely the manifestation of an underlying constitutional abnormality; weight and shape of the couples are not the direct causes of infertility, though weight can affect the hypothalamic-pituitary-ovarian axis. Athletic prowess and pursuits are recognized recently to lower fertility by causing anovulation and amenorrhea.

Occupation and Environment

Fertility rate seemsto be higher among rural population than among urban population, and also higher among those who work by manual labor than among those whose work dependent on mental activity. Many factors contribute to this difference among them that includes differences in their ages at the time of marriage and the differing use of contraception among various social classes. Statistics suggest that fertility is not directly associated with social class. However, several conditions have a predilection for certain classes as for example, endometriosis is more common in higher socioeconomic

classes and pelvic inflammatory disease is more common in lower socioeconomic classes and these relationships are shown in statistics. Also, there is aincreasing trend among professional couples to postpone pregnancy until their careers are established. Increasing attempts to conceive during the periodsof natural decline in fertility and a possible increase in gynecologicalpathology like endometriosis may distort the statistical analysis in future.

Diet

The diet which isas deficient or unbalanced as in anorexia nervosa interferes with ovarian function. Evidences for the role of micronutrients in fertility have been increasing. Zinc and folate deficiency lead to decreased spermatogenesis. The possible mechanism is by defective DNA and RNA synthesis. Deficiency of dietary antioxidants such as beta-carotene, lycopene , retinol and α-tocopherol decrease genital tract secretions in men, leading to infertility especially through immunological mechanisms .

Contraceptives

The role of intra uterine contraceptive devices (IUCDs) as the risk for infertility is controversial. Recently studies suggest that low risk for sexually transmitted infections for IUCD users and hence no additional risk for PID.Congenital abnormalities cause tubal infertility very rarely. They are associated with

endometriosis, corneal fibroid and polyp,urinary tract abnormalities can lead to cornual block or tubal distortion.

Salpingitis isthmicanodosa

It is the nodular thickening of the proximal part of the fallopian tube ,cause for this is not known and it is the rare cause of infertility.

UNEXPLAINED INFERTILITY

Unexplained infertility must be diagnosed only when routine investigations including semen analysis, tubal evaluation and tests for ovulation shows normal results. The incidence of unexplained infertility is 20–30%. Failure of routine tests to detect any obvious contributory factors has led clinicians to speculate about numerous factors contributing to a diagnosis of unexplained infertility.

TREATMENT

Treatment of the infertile couple depends on the cause ,so we must investigate to find out the cause and then go for management .

INVESTIGATIONS

When Infertility should beinvestigated??

A highly fertile couple with regular coitus usually takes an average of about 6-7 months to achieve a pregnancy and four out of five women conceive within 1 year of regular coitus without contraception . Hence, failure to conceive during the first 12-18 months despite regular coitusis accepted to go for full investigation. A strong case can be made for investigating infertility of only one year's duration— especially if the woman is aged over 30 years or the man is aged over 40 years. A clinical examination of both partners, and possibly semen analysis is indicated as soon as any couple becomes worried. An important preliminary to the investigation of infertility is to make certain that the woman is not suffering from a disability which might contraindicate pregnancy or make it undesirable. These conditions are present in 1 percent of women patients seeking advice and it is poor practice to encourage a pregnancy which has to be terminated.

Clinical Assessment of Both Partners

History

The man and wife ideally should be questioned separately and then together, partly to have their evidence corroborated but mainly because either may have something to reveal confidentially. The special points on which information is required are as follows:

- Ages, occupations, previous marriages
- Duration of marriage and the period of time during which contraception has been practised

- Are the partners separated for significant periods of time?
- Previous illnesses and operations. Has the woman had appendicitis, peritonitis, tuberculosis in any site,or any operation on or near the genital tract? Has the man had orchitis , renal disease , bronchiectasis or any operation on or near the genital tract? Has either suffered from gonorrhoea or *Chlamydia* infection or symptoms suggesting them?Severe head injury, meningitis and encephalitis can affect the function of the hypothalamic-pituitary axis.
- The family medical history of each, looking especially for tuberculosis on the woman's side
- Has the woman ever been pregnant by her husband or by another man?
- Has the husband been responsible for pregnancy in another woman?
- Is coitus normal and painless, how frequently is itpractised and at what time in the cycle? Some couples have a wrong idea about the fertile period. More specific questions may be asked about their relationship and details regarding coitus, including erection, ejaculation and penetration.
- Details of menstrual function including factors whichfavour an ovulatory cycle
- Has the woman any other symptoms referred to the genital tract?
- Drugs, e.g. mefenamic acid taken for mittelschmerz pain, may interfere with ovulation. Drugs used for treating hypertension (e.g. guanethidine) may cause impotence and salazopyrine (for ulcerative

colitis) , cytotoxic drugs, immunosuppressives and nitrofurantoin reduce the sperm count.

- Alcohol intake may reduce the potency and frequency of coitus.

Examination

This should cover all systems with particular attentionto the reproductive systems where abnormalities of the penis; cryptorchidism; the size and consistency of the testes and epididymis; the presence of the vasa; a varicocele and any prostatic abnormality in the man; assessment of the vagina; the size, position and mobility of the uterus; and any enlargement or fixation of the adnexa in the woman should be looked for.

In all women with infertility, special attention must be paid to the body habitus, weight, thyroid, breast and note made of the presence of galactorrhoea, acne or hirsutism.

ASSISTED REPRODUCTIVE TECHNOLOGIES

Assisted reproductive technology include In vitro fertilisation , Intra cytoplasmic sperm injection , gamete intrafallopian transfer(GIFT) ,zygote intrafallopian transfer(ZIFT) ,cryopreserved embryo transfers and the use

donor oocytes . The performance of ZIFT and GIFThas declined now days because of the increased success rate of IVF and ICSI[1].

Both involves the following processes

- premature LH surge prevention
- Monitoring of follicular growth
- Pretreatment
- Adjunctive medications
- Triggering of ovulation and oocyte maturation
- Retrieval of oocytes
- Luteal support
- Fertilization either by IVF or ICSI
- In vitro embryo culture
- Transfer of fresh embryo
- Cryopreservation of other surplus embryo
- Monitoring of pregnancy during first trimester

COMPLICATIONS

- Cycle cancellation -6%
- Risks of oocyte retrieval include bleeding requiring transfusion , injury to adjacent structures requiring laparotomy , pelvic abscess formation leading to loss of reproductive function
- Multiple gestation

- Ectopic and heterotopic pregnancy
- Ovarian hyperstimulation syndrome
- Risk of cancer after fertility therapy
- stress

AIM OF THE STUDY

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ULTRASOUND MEASUREMENT OF OVARIAN VOLUME AND ANTRAL FOLLICULAR COUNT IN NORMAL (FERTILITY PROVEN) AND INFERTILE SOUTH INDIAN WOMEN, CHENNAI.

AIMS

(1) To establish the role of AFC as a function of ovarian reserve in fertility-proven and in sub fertile Indian women.

(2) To know the cut-off value of antral follicle count in normal and infertile women.

SETTINGS AND DESIGN

Case-control study

MATERIALS

Transvaginal ultrasound

INCLUSION CRITERIA

CASES

(i) Primary infertility

(ii) No ovarian abnormality (polycystic ovary, ovarian endometriomas) as assessed by transvaginal USG.

(iii) No evidence of uterine malformations or uterine pathology,

(iv) no evidence of endocrinological disease

(v) no evidence of previous ovarian surgery

(vi) no h/o ovulation induction for last 3 months.

CONTROLS

1. Proven natural fertility by having at least one pregnancy carried to term
2. Regular menstrual cycles,
3. No evidence of endocrinological disease,
4. No evidence of ovarian surgery,
5. No ovarian abnormality as assessed by transvaginal USG, and

EXCLUSION CRITERIA

i. any H/O ovarian abnormality like polycystic ovary, ovarian endometriomas

ii. History and any evidence of uterine malformations or uterine pathology,

iii. H/o endocrinological disease, and

iv. H/o previous ovarian surgery

v. Hormonal contraception stopped > 3 months before entering the study protocol.

vi. H/o ovulation induction for last 3 months.

SAMPLE SIZE

Sample size for frequency in a population – 30 cases and 30 controls

SAMPLINGMETHODS

- All the patients attending gynecologyoutpatient department in reproductive age group (25-35yrs) who are all undergoing workup for infertility are included.
- They were all compared to equal number of controls(fertility proven) in same age group(25-35yrs).
- The basal ovarian volume and AFC were measured by endovaginal ultrasound.
- Transvaginal USG was carried out on the second or third day of the menstrual cycle.
- Thorough survey of each ovary was done by scanning from the outer to the inner margin.

- All follicles having adequate morphology as described for a healthy follicle (i.e., 2-10 mm size range of well-defined anechoic cysts with smooth margins and absence of internal septations or nodularity) were measured and counted in each ovary. The sum of follicular count in both ovaries was labeled as Antral follicular count.
- The ovaries are measured in three planes and the ovarian volume was calculated using the prolate ellipsoid formula V=D1xD2xD3x0.523. D1, D2 ,D3 are the three maximal longitudinal antero-posterior and transverse diameters respectively.

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

ROC CURVE FOR VARIABLES IN RELATION TO INFERTILITY

Comparison of ROC curves

Variable 1	Age Age
Variable 2	BMI BMI
Variable 3	OVARIAN VOLUME OVARIAN VOLUME
Variable 4	AFC
Classification variable	GROUP

Sample size		60
Positive group :	GROUP = 1	30
Negative group :	GROUP = 0	30

Group 1 – infertile group

Group 0 – control group

	AUC	SE[a]	95% CI[b]
AFC	0.980	0.0105	0.905 to 0.999
OVARIAN_VOLUME	0.562	0.0757	0.428 to 0.690
BMI	0.557	0.0761	0.423 to 0.685
AGE	0.672	0.0697	0.539 to 0.788

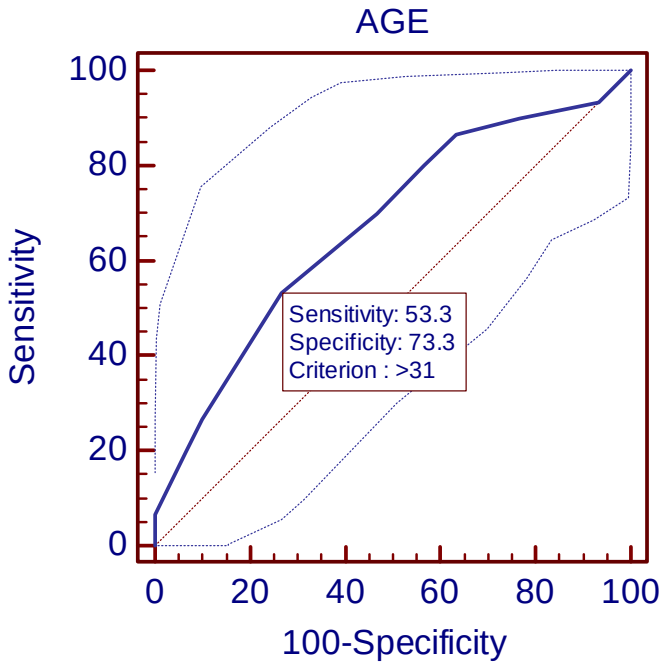
AUC –area under the curve

SE - Standard error

CI –confidence interval

Variable 1

AGE DISTRIBUTION



AREA UNDER ROC curve - 0.67222

STATISTICAL SIGNIFICANCE P - 0.0134(<0.05)

Hence age is the significant variable to determine infertility with p value of 0.05

Variable	AGE
Classification variable	GROUP

Sample size		60
Positive group :	GROUP = 1	30
Negative group :	GROUP = 0	30

Disease prevalence (%)	Unknown

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.672222
Standard Error[a]	0.0697
95% Confidence interval[b]	0.538881 to 0.787914
z statistic	2.472
Significance level P (Area=0.5)	0.0134

[a] DeLong et al., 1988

[b] Binomial exact

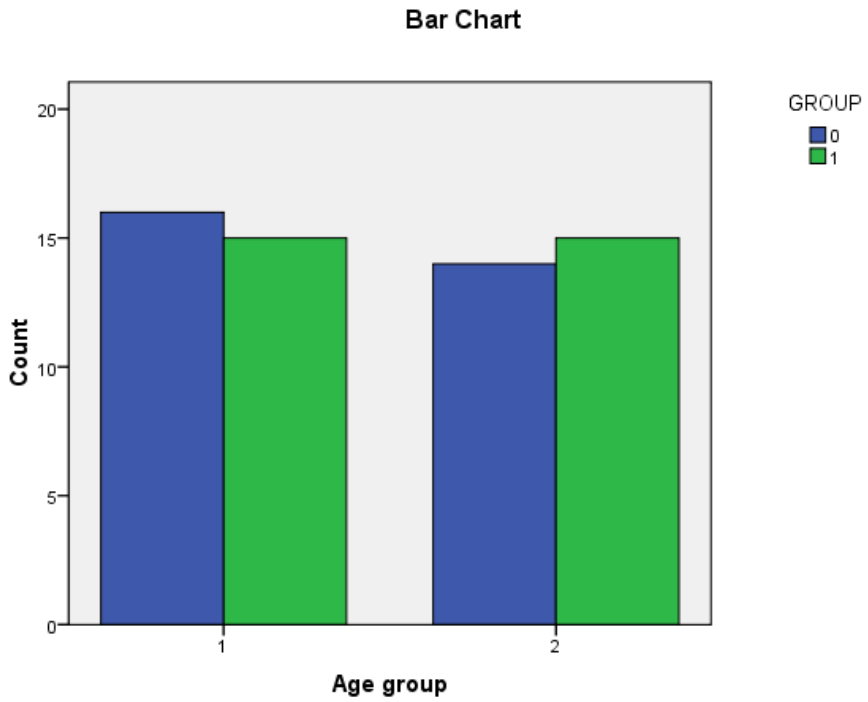
Youden index

Youden index J	0.2667
Associated criterion	>31

AGE GROUP #GROUP

Crosstab

			GROUP		
			0	1	Total
Age group	25-31	Count	16	15	31
		% within Age group	51.6%	48.4%	100.0%
		% within GROUP	53.3%	50.0%	51.7%
		% of Total	26.7%	25.0%	51.7%
	31-35	Count	14	15	29
		% within Age group	48.3%	51.7%	100.0%
		% within GROUP	46.7%	50.0%	48.3%
		% of Total	23.3%	25.0%	48.3%
	Total	Count	30	30	60
		% within Age group	50.0%	50.0%	100.0%
		% within GROUP	100.0%	100.0%	100.0%
		% of Total	50.0%	50.0%	100.0%



Age Group 1 – 25– 30yrs

Group 2 - 31 -35 yrs

Among infertile group 15 in group 1 , 15 in group 2

Among control group 16 in group 1 , 14 in group 2

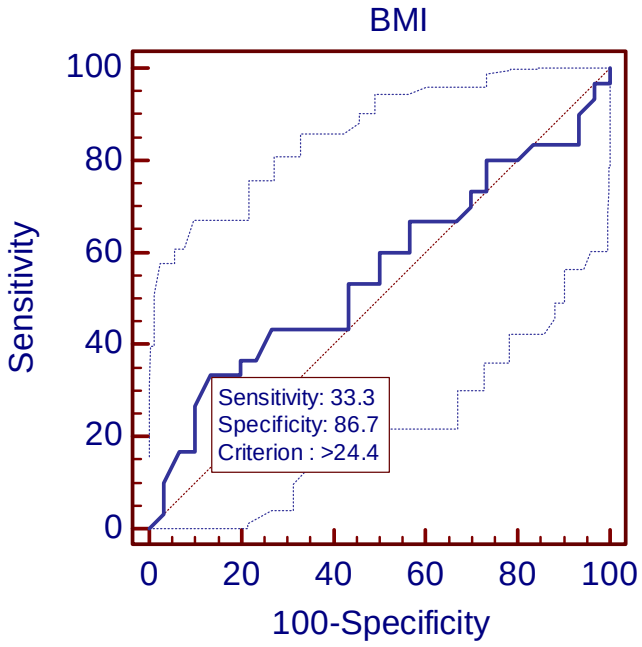
We also got the mean standard deviation of the both infertile and control group and found that there exists a statistical significance among the two groups with response to age

Group statistics

group	n	mean	Standard deviation	Standard error mean	Significance p
Age 1(infertile)	30	31.30	2.466	0.450	0.019
0(control)	30	29.80	2.355	0.430	0.019

Variable 2

BMI



AREA UNDER ROC curve – 0.556667

SIGNIFICANT LEVEL P - 0.4568(>0.05)

Hence BMI is not a significant variableto determine infertility with significant level >0.05

Variable	BMI BMI

Classification variable	GROUP

Sample size		60
Positive group :	GROUP = 1	30
Negative group :	GROUP = 0	30

Disease prevalence (%)	unknown

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.556667
Standard Error[a]	0.0761
95% Confidence interval[b]	0.422619 to 0.684931
z statistic	0.744
Significance level P (Area=0.5)	0.4568

[a] DeLong et al., 1988
[b] Binomial exact

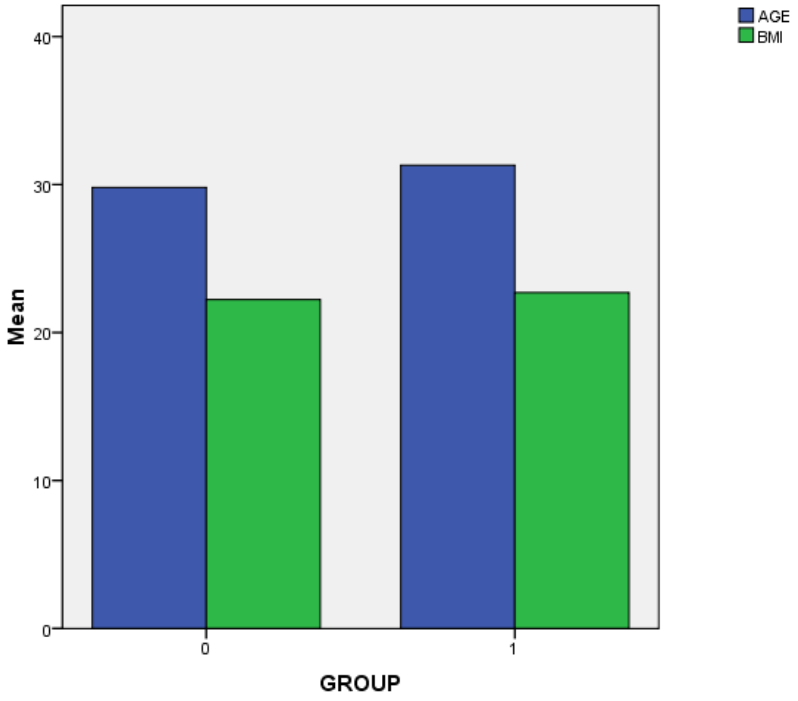
Youden index

Youden index J	0.2000
Associated criterion	>24.4

BMI GROUP * GROUP

Crosstab

			GROUP		
			0	1	Total
BMI GROUP	1	Count	27	25	52
		% within BMI GROUP	51.9%	48.1%	100.0%
		% within GROUP	90.0%	83.3%	86.7%
		% of Total	45.0%	41.7%	86.7%
	2	Count	3	5	8
		% within BMI GROUP	37.5%	62.5%	100.0%
		% within GROUP	10.0%	16.7%	13.3%
		% of Total	5.0%	8.3%	13.3%
	Total	Count	30	30	60
		% within BMI GROUP	50.0%	50.0%	100.0%
		% within GROUP	100.0%	100.0%	100.0%
		% of Total	50.0%	50.0%	100.0%



BMI Group 1 – <25

Group 2 - ≥25

Among infertile group 25 in group 1 , 5 in group 2

Among control group 27 in group 1 , 3 in group 2

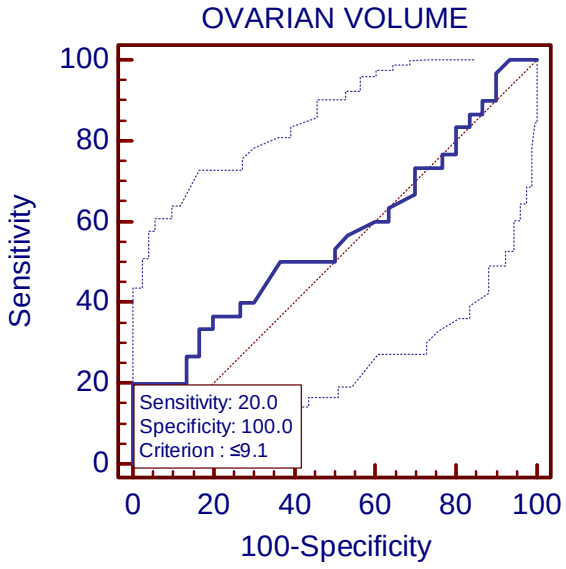
We also got the mean standard deviation of the both infertile and control group and found that there is no statistical significance among the two groups with response to BMI

Group statistics

group	n	mean	Standard deviation	Standard error mean	Significance p
BMI 1(infertile)	30	22.70	2.672	0.488	0.452
0(control)	30	22.22	2.194	0.401	0.452

Variable 3

OVARIAN VOLUME



Area under ROC curve – 0.562222

SIGNIFICANT LEVEL P – 0.4113(>0.05)

HENCE ovarian volume is not a significant variable to determine infertility

Variable	OVARIAN_VOLUME OVARIAN VOLUME
Classification variable	GROUP

Sample size		60
Positive group :	GROUP = 1	30
Negative group :	GROUP = 0	30

Disease prevalence (%)	unknown

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.562222
Standard Error[a]	0.0757
95% Confidence interval[b]	0.428052 to 0.690041
z statistic	0.822
Significance level P (Area=0.5)	0.4113

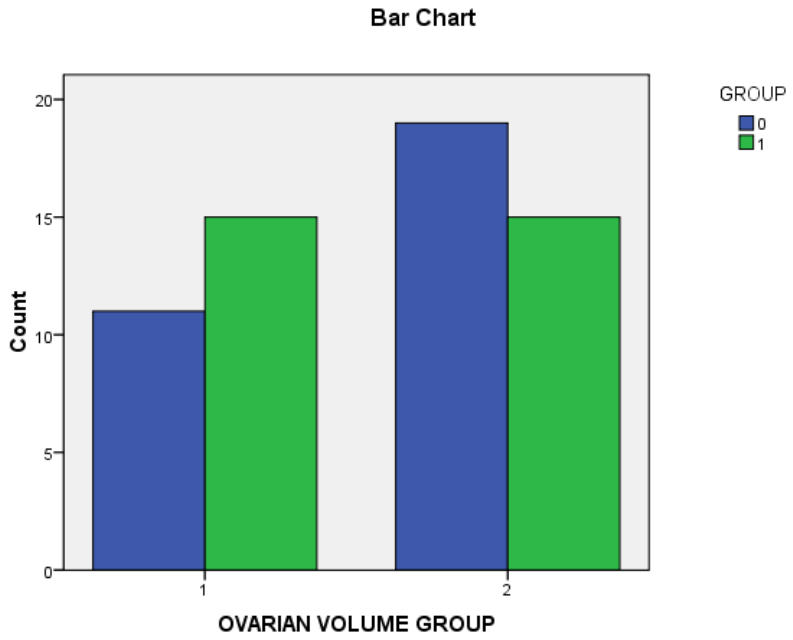
[a] DeLong et al., 1988
[b] Binomial exact

Youden index

Youden index J	0.2000
Associated criterion	≤9.1

OVARIAN VOLUME GROUP * GROUP Crosstabulation

			GROUP		
			0	1	Total
OVARIAN VOLUME GROUP	1	Count	11	15	26
		% within OVARIAN VOLUME GROUP	42.3%	57.7%	100.0%
		% within GROUP	36.7%	50.0%	43.3%
		% of Total	18.3%	25.0%	43.3%
	2	Count	19	15	34
		% within OVARIAN VOLUME GROUP	55.9%	44.1%	100.0%
		% within GROUP	63.3%	50.0%	56.7%
		% of Total	31.7%	25.0%	56.7%
	Total	Count	30	30	60
		% within OVARIAN VOLUME GROUP	50.0%	50.0%	100.0%
		% within GROUP	100.0%	100.0%	100.0%
		% of Total	50.0%	50.0%	100.0%



OVARIAN VOLUME Group 1 – 9-11

Group 2 - ≥11

Among infertile group 15 in group 1 ,15 in group 2

Among control group 11 in group 1 , 19 in group 2

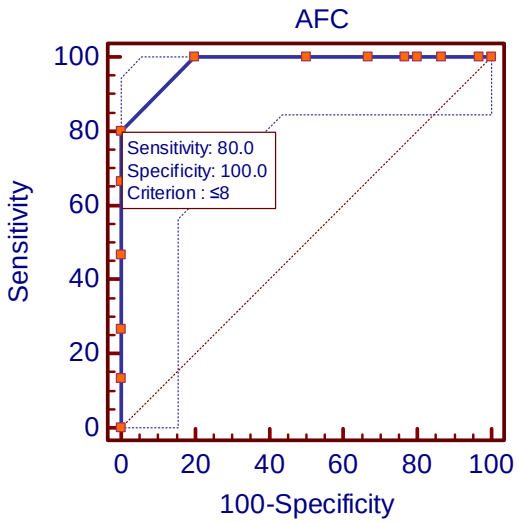
We also got the mean standard deviation of the both infertile and control group and found that there is no statistical significance among the two groups with response to OVARIAN VOLUME

Group statistics

group	n	mean	Standard deviation	Standard error mean	Significance p
Ovarian Volume 1(infertile)	30	10.86	1.639	0.299	0.184
0(control)	30	11.36	1.211	0.221	0.185

Variable4

ANTRAL FOLLICULAR COUNT



Area under ROC curve – 0.980000

Significant level p - <0.0001

Hence AFC is a significant variable to determine infertility with significant value of <0.05

Variable	AFC AFC
Classification variable	GROUP

Sample size		60
Positive group :	GROUP = 1	30
Negative group :	GROUP = 0	30

Disease prevalence (%)	unknown

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.980000
Standard Error[a]	0.0105
95% Confidence interval[b]	0.905212 to 0.999144
z statistic	45.695
Significance level P (Area=0.5)	<0.0001

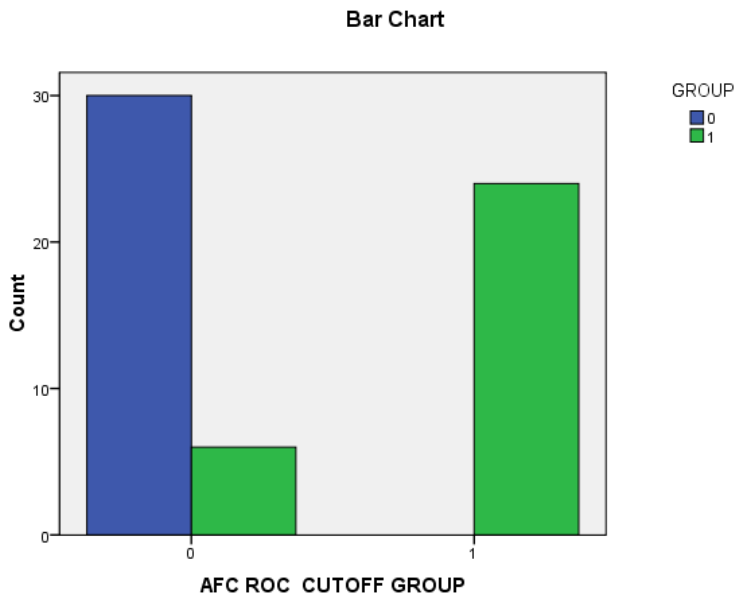
[a] DeLong et al., 1988
[b] Binomial exact

Youden index

Youden index J	0.8000
Associated criterion	≤8

AFC ROC CUTOFF GROUP * GROUP Crosstabulation

			GROUP		
			0	1	Total
AFC ROC CUTOFF GROUP	0	Count	30	6	36
		% within AFC ROC CUTOFF GROUP	83.3%	16.7%	100.0%
		% within GROUP	100.0%	20.0%	60.0%
		% of Total	50.0%	10.0%	60.0%
	1	Count	0	24	24
		% within AFC ROC CUTOFF GROUP	.0%	100.0%	100.0%
		% within GROUP	.0%	80.0%	40.0%
		% of Total	.0%	40.0%	40.0%
	Total	Count	30	30	60
		% within AFC ROC CUTOFF GROUP	50.0%	50.0%	100.0%
		% within GROUP	100.0%	100.0%	100.0%
		% of Total	50.0%	50.0%	100.0%



AFI Group 0 – >8

Group 1- ≤8

Among infertile group 6 in group 0 , 24 in group 1

Among control group 30in group 0 , 0 in group 1

We also got the mean standard deviation of the both infertile and control group and found that there exists a statistical significance among the two groups with response to antral follicular count

Group statistics

group	n	mean	Standard deviation	Standard error mean	Significance p
AFC 1(infertile)	30	6.67	1.688	0.308	0.000
0(control)	30	11.23	2.112	0.386	0.000

Chi-Square Tests

	Value	Exact Sig. (2-sided)
McNemar Test		.031[a]
N of Valid Cases	60	

a. Binomial distribution used.

Parameter	Estimate	Lower - Upper 95% CIs	Method
Sensitivity	80%	(62.69, 90.5[1])	Wilson Score
Specificity	100%	(88.65, 100[1])	Wilson Score
Positive Predictive Value	100%	(86.2, 100[1])	Wilson Score
Negative Predictive Value	83.33%	(68.11, 92.13[1])	Wilson Score
Diagnostic Accuracy	90%	(79.85, 95.34[1])	Wilson Score
Cohen's kappa (Unweighted)	0.8	(0.5521 - 1.048)	

Symmetric Measures

		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	.800	.076	6.325	.000
	N of Valid Cases	60			

Above table shows the cohen's kappa agreement of 0.8 , it means that there is very good kappa agreement for infertility as we expected with response to antral follicular count

Correlation of different variables with antral follicular count in both groups separately described below

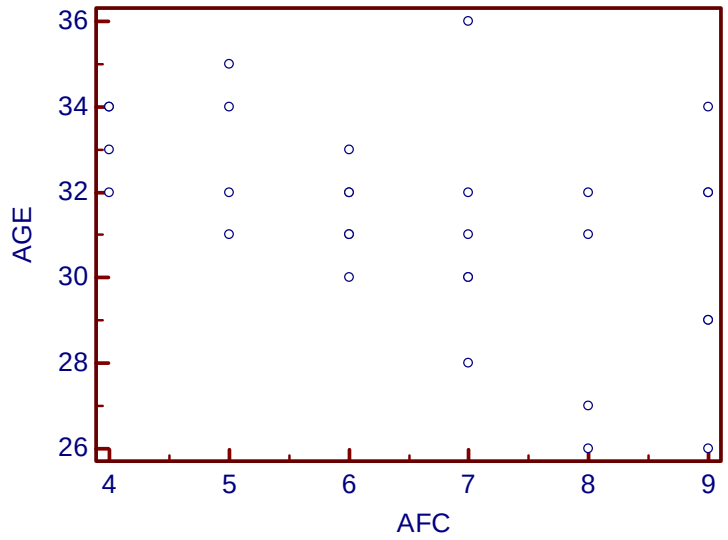
Correlation INFERTILE GROUP

AGE # AFC

Variable Y	AGE
Variable X	AFC AFC

Sample size	30
Correlation coefficient r	-0.4887
Significance level	P=0.0061
95% Confidence interval for r	-0.7219 to -0.1559

Scatter diagram



There existing a significant correlation between age and antral follicular count with significant level of 0.0061

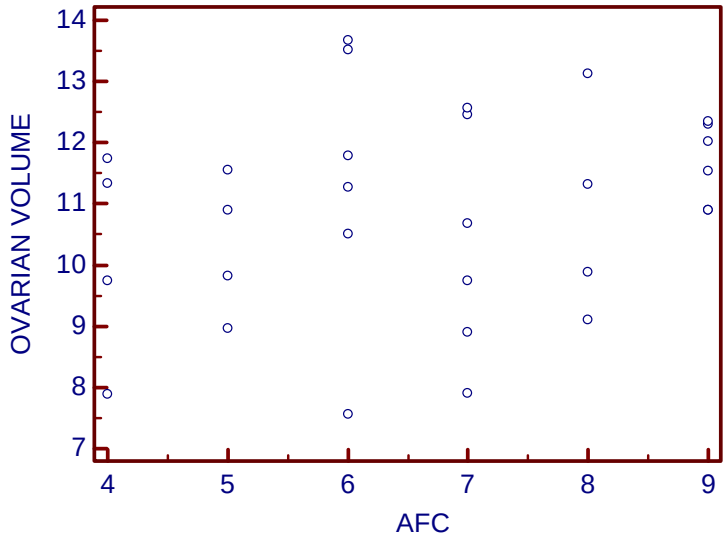
Correlation

OVARIAN VOLUME #AFC

Variable Y	OVARIAN_VOLUME OVARIAN VOLUME
Variable X	AFC AFC

Sample size	30
Correlation coefficient r	0.2385
Significance level	P=0.2044
95% Confidence interval for r	-0.1332 to 0.5514

Scatter diagram



There is no association between ovarian volume and antral follicular count in the infertile group with significany level of 0.2044

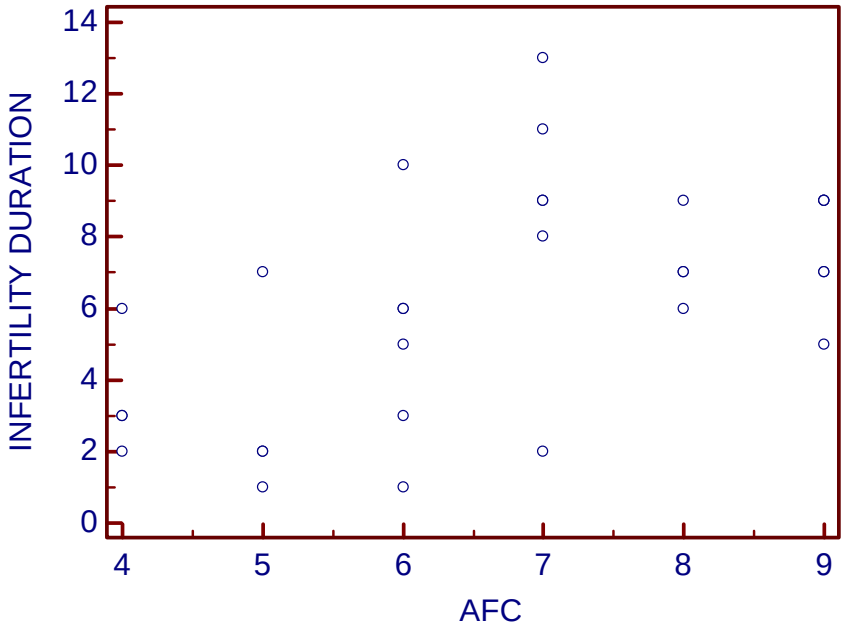
Correlation

INFERTILITY DURATION # AFC

Variable Y	INFERTILITY_DURATION INFERTILITY DURATION
Variable X	AFC AFC

Sample size	30
Correlation coefficient r	0.5460
Significance level	P=0.0018
95% Confidence interval for r	0.2312 to 0.7573

Scatter diagram



There existing a significant correlation between infertility duration and antral follicular count in infertile group with the significant level of 0.0018

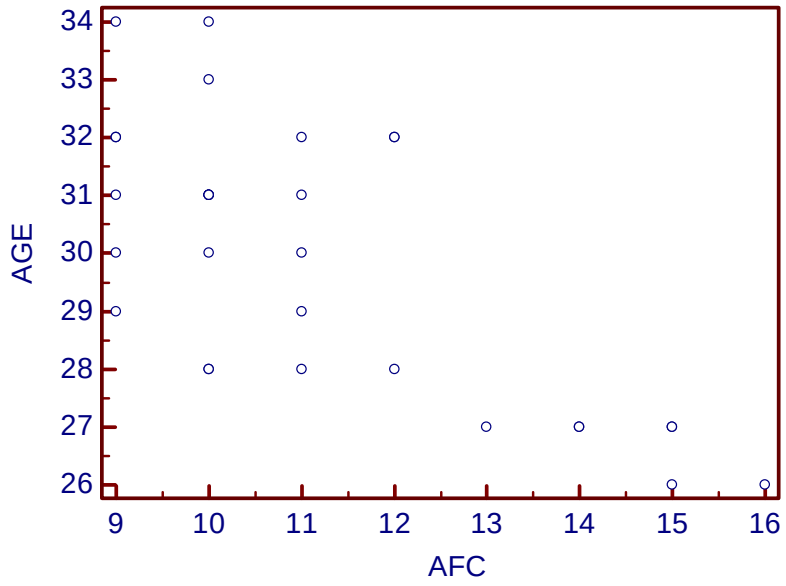
Correlation(CONTROL GROUP)

AGE # AFC

Variable Y	AGE
Variable X	AFC AFC

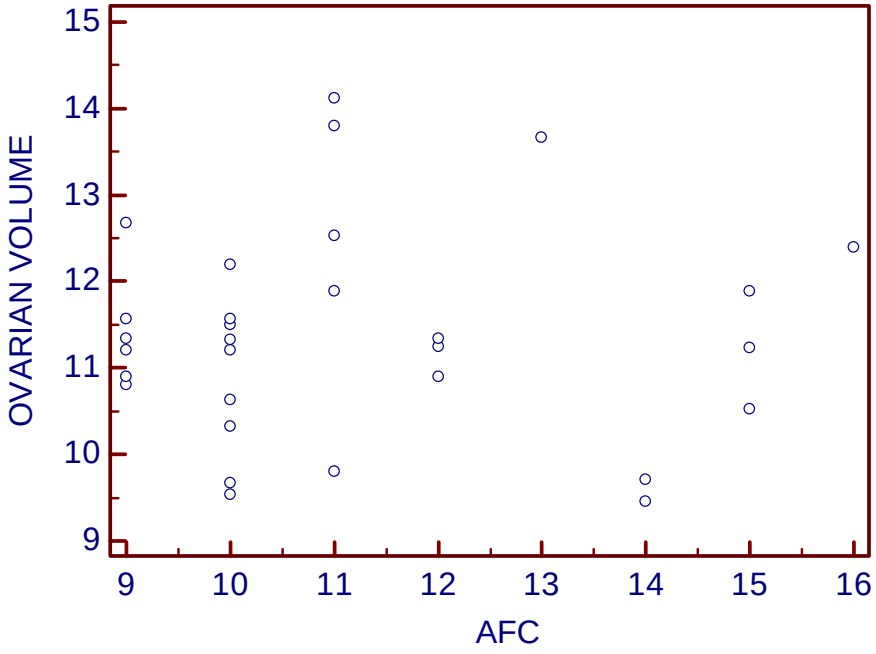
Sample size	30
Correlation coefficient r	-0.7183
Significance level	P<0.0001
95% Confidence interval for r	-0.8568 to -0.4830

Scatter diagram



Here in control group also there existing a significant correlation between age and antral follicular count with significant level of <0.0001

OVARIAN VOLUME #AFC



Correlation

Variable Y	OVARIAN_VOLUME OVARIAN VOLUME
Variable X	AFC AFC

Sample size	30
Correlation coefficient r	0.005794
Significance level	P=0.9758
95% Confidence interval for r	-0.3552 to 0.3653

Scatter diagram

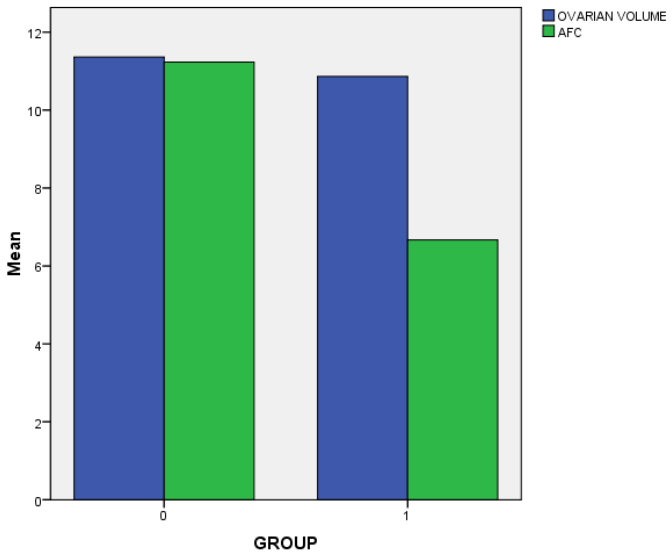
Here in control group also there is no significant correlation between ovarian volume and antral follicle count

RESULT

Comparative analysis of biophysical and sonographic variables in infertile and fertile patients

VARIABLES	CASES(n=30) (Mean±SD)	CONTROLS(N=30) (Mean±SD)	P Value
AGE(years)	31.30±2.466	29.80±2.355	**0.0134**
BMI(kg/m^2)	22.70±2.672	22.22±2.194	0.4568
Antral follicle count(AFC)	6.67±1.688	11.23±2.112	**0.0001**
Total ovarian volume(cc)	10.86±1.639	11.36±2.112	0.4113

BMI-Body mass index, SD-standard deviation



The above bar chart shows that there is no change in ovarian volume in both cases and controls but there is significant change in antral follicular count in both group with **cut off value of 8**

DISCUSSION

DISCUSSION

Limited data is available on ovarian ageing in the sub-fertile and healthy population and the role of sonographic biomarkers (AFC, ovarian volume) of ovarian reserve. Most of the available data is based on studies outside India. The present study evaluates the relationship of AFC with age and BMI in sub-fertile cases and with healthy controls. Role of ovarian volume is also evaluated and compared with AFC.

My observation indicates that the number of antral follicles is lower in sub-fertile patients than in fertile group (25 -35 yrs), in view of the significantly lower median AFC in women of the former group ($P<0.001$). The range of AFC in females presenting with complaints of infertility was 4-12(median value of 8). The cut off value in Indian women is at a lower base line than that noted in the western literature. This variability in the value of AFC is most probably due to the differences in the ratio, socio-economic and geographic background of Indian and Western populations.

Though the reproductive ability of a woman is directly related to the remaining pool of primordial follicles at a particular point of time. This stock depletes as age progresses and is completely exhausted at menopause. Hence it may be reasonable to assume that the number of antral follicles reflects the

ovarian pool and indirectly the reproductive age. My data shows that there is an inverse relation between AFC and the age of female (A negative correlation value r= -0.4887 with p=0.0061). The sensitivity of AFC to identify poor responders before induction of ovulation with exogenous gonadotrophins has been found to be around 89% in previous studies.

I however did not endeavor to establish any such correlation in our population as the same was out of scope of the study. I submit that the good correlation shown by my data between the afore mentioned parameters may be used in future by other Indian groups, evaluating metrics for patient selection during planning of ovulation induction. On evaluating antral follicles up to 10mm in diameter, significant difference in numbers was noted in my study population(6.67±1.688 in cases; 11.23 ± 2.112 in controls; p value of <0.0001). A cut off value of 8 follicles (aggregrate of both ovaries) may be taken as a standard for successful pregnancy outcome.

Inter-group comparison of median values of ovarian volume showed no significant difference in my study. This parameter however can be routinely measured without any added effort along with AFC. Though my data reflects that ovarian volume has no role as a bio marker of ovarian reserve, I would like to suggest routine recording and further evaluation of role of this parameter in population based data sets.

LIMITATIONS

LIMITATIONS

The major limitation of my study is its cross-sectional nature. Hence I could not conclusively establish the fact that lower AFC actually results in infertility. In addition while lower AFCs are seen among sub-fertile women at the time of presentation it could be ascertained from my data if this results from a smaller initial oocyte pool or an accelerated rate of loss. Longitudinal studies of AFC in both fertile and sub-fertile women will be necessary to determine the predictive value of AFC for future fertility.

Threshold values that predict a very low likelihood of spontaneous conception may be identified and thus the non-specific term “diminished ovarian reserve” currently overused in the infertility literature could gain clinical relevance among the general population. Pre ART (Artificial Reproductive Technique) ultrasonographic AFC has been shown to be an excellent predictor of ovarian reserve and response, with significant superiority in relation to other markers. Results from literature seem to converge for recognition of importance of AFC as a predictor of ovarian response.

CONCLUSION

CONCLUSION

- The results of this study indicate that AFC is a viable predictor of fecundity in South Indian women of child bearing age in terms of capability to conceive on a two point scale (i.e. positive or negative).

- The mean AFC in South Indian women is significantly different from that noted in Western literature, mainly due to racial, geographic and socio-economic reasons.

- A cut off value of 8 may be used to prognosticate patients undergoing assessment for female factor infertility.

- On the other hand same data can be utilized for optimum patient selection for ART. This would in turn lead to a higher success rate of this technique.

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MASTERCHART

NO	GROUP	OP NO	NAME	AGE	Age group	Married since	INFERTILITY DURATION	MENSTRUAL HISTORY	OTHER INFERTILITY FACTORS	BMI	BMI GROUP	OVARIAN VOLUME	AFC
	0	1145	PRIYA	31	2	5		REG		21.13	1	11.32	10
	0	2535	DEVI	31	2	3		REG		22.78	1	10.63	10
	0	1098	AMIRTHAM	26	1	4		REG		19.23	1	10.53	15
	0	4356	REVATHI	26	1	4		REG		20.45	1	12.4	16
	0	4888	FAIROZ	27	1	7		REG		19.8	1	11.89	15
	0	546	KALA	27	1	6		REG		19.89	1	9.45	14
	0	5677	GEETHA	27	1	7		REG		21.5	1	11.23	15
	0	5245	BALA NIRMALA	27	1	4		REG		23.5	1	9.71	14
	0	1167	RANI	27	1	3		REG		27.89	2	13.67	13
	0	4367	MANIMEGALAI	28	1	4		REG		20.45	1	11.24	12
	0	325	MALA	28	1	3		REG		22.4	1	11.89	11
	0	1542	MUTHULAKSHMI	28	1	6		REG		23.45	1	11.21	10
	0	1887	BABY	28	1	4		REG		24.4	1	9.54	10
	0	2356	DEEPA	29	1	10		REG		19.8	1	10.81	9
	0	4356	REKHA	29	1	8		REG		21.5	1	13.8	11
	0	8789	GOWTHAMI	30	1	10		REG		18.7	1	9.67	10
	0	3455	JAYANTHI	30	1	6		REG		20.98	1	12.67	9

	0	985	LAKSHMI	30	1	5		REG		22.89	1	9.8	11
	0	2145	NEETHU	31	2	5		REG		19.8	1	11.56	10
	0	1269	MARAGATHAM	31	2	5		REG		21.32	1	12.53	11
	0	5287	PAAPA	31	2	6		REG		23.8	1	11.5	10
	0	6247	THILAGA	31	2	11		REG		26.4	2	11.56	9
	0	7388	KANAGA	32	2	8		REG		21.1	1	10.9	12
	0	2469	AMMU	32	2	7		REG		23.4	1	11.34	12
	0	6578	YASMIN	32	2	12		REG		23.4	1	11.21	9
	0	663	VASUKI	32	2	7		REG		23.4	1	11.34	9
	0	2009	MUTHU	32	2	4		REG		25.56	2	14.12	11
	0	5774	DIVYA	33	2	7		REG		22.4	1	12.19	10
	0	234	JEEVA	34	2	6		REG		20.89	1	10.32	10
	0	528	SELVI	34	2	6		REG		24.5	1	10.9	9
1	1	9871	MEENA	32	2	2	1	REG	NIL	20.54	1	13.52	6
2	1	2137	RANI	31	2	3	2	REG	NIL	24.5	1	9.75	7
8	1	2213	AMMU	31	2	8	7	REG	NIL	24.65	1	13.12	8
3	1	3214	AMUDHA	32	2	2	1	REG	NIL	19.23	1	11.74	4
4	1	3331	PUSHPA	32	2	4	3	REG	NIL	21.63	1	11.27	6
7	1	7861	DEEPA	33	2	7	6	REG	NIL	26.4	2	7.56	6
15	1	4356	LEELA	26	1	5	4	REG	NIL	23.56	1	10.9	9
24	1	2336	HARITHRA	26	1	9	7	REG	NIL	20.98	1	10.9	9
27	1	1235	MEERA	26	1	7	6	REG	NIL	21.45	1	9.1	8
9	1	1234	PAAPA	27	1	8	7	REG	NIL	19.63	1	12.02	9
10	1	7658	GEETHA	27	1	6	5	REG	NIL	20.9	1	11.54	9
23	1	3265	JAWAHAR	27	1	10	9	REG	NIL	23.45	1	9.89	8
16	1	4368	VATHI	28	1	6	3	REG	NIL	24.5	1	11.32	8

26	1	4374	NISHA	28	1	10	9	REG	NIL	24.56	1	12.45	7
11	1	7644	RUKMANI	29	1	7	4	REG	NIL	19.45	1	12.56	7
20	1	4687	PRABHA	29	1	10	9	REG	NIL	19.89	1	12.34	9
28	1	4442	LAKSHMI	29	1	6	5	REG	NIL	23.45	1	12.3	9
5	1	1437	RAJI	30	1	7	4	REG	NIL	22.54	1	10.68	7
21	1	6437	DEVI	30	1	14	13	REG	NIL	18.98	1	8.9	7
25	1	6238	DHARINI	30	1	7	6	REG	NIL	22.67	1	11.78	6
29	1	4565	SATHYA	30	1	12	11	REG	NIL	22.34	1	7.9	7
30	1	4587	MEENA	31	2	11	10	REG	NIL	22.56	1	10.5	6
	1	6244	SARASWATHI	31	2	11	7	REG		26.4	2	11.56	5
	1	1110	STELLA	31	1	6	5	REG		27.89	2	13.67	6
6	1	1124	MALAR	32	2	5	3	REG	NIL	18.12	1	9.74	4
13	1	7488	JAYANTHI	32	2	4	3	REG	NIL	20.56	1	7.89	4
19	1	4743	PRASANA	32	2	3	2	REG	NIL	24.56	1	10.9	5
18	1	6849	INIYA	33	2	4	3	REG	NIL	27.5	2	11.34	4
17	1	8743	SARASU	34	2	3	2	REG	NIL	26.7	2	9.82	5
14	1	6839	VASUKI	35	2	2	1	REG	NIL	21.45	1	8.97	5

ANNEXURES

CONSENT FORM

நோயாளிஒப்புதல்படிவம்

B ´ Ä ö \ ´ ¯ ¨ £ k ® u ø » ¨ ¦ :**ULTRASOUND MEASUREMENT OF OVARIAN VOLUME AND ANTRAL FOLLICULAR COUNT IN NORMAL (FERTILITY –PROVEN) AND INFERTILE SOUTH INDIAN WOMEN (CHENNAI)**

Department of Obstetrics and Gynaecology, KMCH.

நோயாளியின்பெயர் நோயாளியின்வயது

பதிவுஎண்

நோயாளிகீழ்கண்டவற்றுள்கட்டங்களை செய்யவும்

- மேற்குறிப்பிட்டுள்ளஆராய்ச்சியின்நோக்கத்தையும்பயனையும்முழுவதுமாகபுரிந்துகொண்டேன் ☐
- மேலும்எனதுஅனைத்துசந்தேகங்களையும்கேட்டுஅதற்கானவிளக்கங்களையும்தெளிவுபடுத்திக்கொண்டேன்
- மேலும்இந்தஆராய்ச்சிக்குஎனதுசொந்தவிருப்பத்தின்பேரில்பங்கேற்கிறேன் என்றும் ☐
- மேலும்எந்தநேரத்திலும்எவ்விதமுன்னறிவிப்புமின்றிஇந்தஆராய்ச்சியிலிருந்துவிலகமுழுமையானஉரிமைஉள்ளதையும்
- இதற்குஎவ்விதசட்டபிணைப்பும்இல்லைஎன்பதையும்அறிவேன்
- ஆராய்ச்சியாளரோ ஆராய்ச்சிஉதவியாளரோ ஆராய்ச்சிஉபயத்தாரோ ஆராய்ச்சிபேராசிரியரோ
- ஒழுங்குநெறிசெயற்குழுஉறுப்பினர்களோஎப்போதுவேண்டுமானாலும்எனது அனுமதியின்றிஎனதுஉள்நோயாளிபதிவுகளைஇந்தஆராய்ச்சிக்காகவோஅல்லதுஎதிர்காலபிறஆராய்ச்சிகளுக்காகவோபயன்படுத்திக்கொள்ளலாம்என்றும் ☐
- மேலும்இந்தநிபந்தனைநான்இவ்வாரய்ச்சியிலிருந்துவிலகினாலும்தகும்என்றும்ஒப்புக்கொள்கிறேன்
- ஆயினும்எனதுஅடையாளம்சம்பந்தப்பட்டஎந்தபதிவுகளும் சட்டபூர்வமானதேவைகள்தவிர வெளியிடப்படமாட்டாதுஎன்றஉறுதிமொழியின்பெயரில்இந்தஆராய்ச்சியிலிருந்துகிடைக்கப்பெறும்முடிவுகளைவெளியிடமறுப்புதெறிவிக்கமாட்டேன்என்றுஉறுதியளிக்கின்றேன்
- இந்தஆராய்ச்சிக்குநான்முழுமனதுடன்சம்மதிக்கின்றேன்என்றும்மேலும்ஆராய்ச்சிக்குழுவினர்எனக்குஅளிக்கும்அறிவுரைகளைதவறாதுபின்பற்றுவேன்என்றும்இந்தஆராய்ச்சிகாலம்முழுவதும்எனதுஉடல்நிலையில்ஏதேனும் மாற்றமோஅல்லதுஎதிர்பாராதபாதகமானவிளைவோஎற்படுமாயின்உடனடியாகஆராய்ச்சிகுழுவினரைஅணுகுவேன்என்றும்உறுதியளிக்கின்றேன் ☐
- இந்தஆராய்ச்சிக்குத்தேவைப்படும்அனைத்துமருத்துவப்பரிசோதனைகளுக்கும்ஒத்துழைப்புதருவேன்என்றுஉறுதியளிக்கின்றேன் ☐
- இந்தஆராய்ச்சிக்குயாருடையவற்புருத்தலுமின்றிஎனதுசொந்தவிருப்பத்தின் பேரிலும்சுயஅறிவுடனும்முழுமனதுடனும்சம்மத்திக்கின்றேன்என்றுஇதன் மூலம்ஒப்புக்கொள்கிறேன் ☐
- இடம் தேதி

நோயாளியின்கையொப்பம்பெருவிரல்கைரேகை ஆராய்ச்சியாளரின்கையொப்பம்

PROFORMA

NAME HUSBAND NAME

AGE AGE

IP NO QUALIFICATION

OCCUPATION

ADDRESS

SOCIOECONOMIC STATUS

QUALIFICATION

HEIGHT

WEIGHT

BMI

COMPLAINTS IF ANY MENSTRUAL HISTORY:-

MARIETAL HISTORY :-

OBSTETRIC HISTORY :-

ANDROLOGICAL HISTORY :-

COITAL HISTORY :-

PAST HISTORY :-

PERSONAL HISTORY :-

FAMILY HISTORY :-

GENERAL EXAMINATION:-

HEIGHT WEIGHT

GAIT BREAST THYROID

ABDOMINAL EXAMINATION

PER SPECULUM EXAMINATION

PER VAGINAL EXAMINATION

PER RECTAL EXAMINATION

INVESTIGATIONS

1. BASIC INVESTIGATIONS
2. DIAGNOSTIC HYSTERO LAPAROSCOPY / HYSTERO SALPHINGOGRAPHY
3. THYROID FUNCTION TEST
4. URINE CULTURE AND SENSITIVITY
5. HIGH VAGINAL SWAB CULTURE AND SENSITIVITY
6. TRANS VAGINAL ULTRA SOUND
7. SEMEN ANALYSIS